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Table of Contents on 3rd Cover

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The Journal of Pediatrics

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TREATMENT OF ACUTE LEUKEMIA IN CHILDREN WITH AND WITHOUT FOLIC ACID ANTAGONISTS

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THE administration of folic acid antagonists for the treatment of acute leukemia in children by Farber and his associates[1] gave responses which suggested that the number of temporary remissions was greater than previously reported with other forms of treatment. Since any advances in understanding the etiology of this disease may be dependent upon the use of those drugs that provide clinical improvement, we endeavored to study responses in our series with this single group of therapeutic substances. The effects of Aminopterin and A-methopterin on a series of patients with acute leukemia were compared to case records of those children treated prior to the advent of the folic acid antagonists. The clinical responses were in general sufficiently encouraging to suggest that metabolic studies be done to determine why the dysplastic bone marrow and cellular immaturity were temporarily corrected by the administration of the antagonists. The results of the clinical studies are reported here and the metabolic findings are the subject of another report.

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THE DATA

A selected group of forty-eight cases of acute leukemia in children of various ages admitted to the Research and Educational Hospitals of the University of Illinois during the past twenty years has been reviewed in detail (Group A). These patients were selected on the basis of completeness of data and close personal observation of their clinical course. The cases were observed during the years when a variety of therapeutic agents were employed in the management of the leukemic child. Arsenicals, nitrogen mustard, urethane, x-ray, or radioactive phosphorus were given individually to some of the patients, but as a group these cases can be considered as "pre-antagonist" cases. The second group of thirty-eight patients (Group B) was observed from the spring of 1948 through August, 1951, and will be referred to as the "antagonist-treated" group. At least three of our patients survived more than two years, one of these is now well through his third year of remission. The thirty-eight patients treated in the three-year "antagonist period" would ordinarily bespeak a greater incidence of the disease in recent years, but it may be that today diagnoses are more readily made

and our interest in such cases attracted a greater number to our clinic and hospital. Each of our outpatient cases was observed by us twice weekly or weekly, or at intervals which varied with the course of the individual case. Frequent blood and bone marrow studies were done on both hospitalized patients and outpatients. Several patients were hospitalized for months while they were being studied, one for as long as two years.

Several problems arise in the consideration of any new therapeutic agent in the management of acute leukemia. Whether spontaneous remissions occur frequently enough to give falsely encouraging results, which would be attributed to any new medication, is a factor that must be determined in the evaluation of any therapy. The question dealing with spontaneous remissions in leukemia has been reviewed by Dreyfus[2] who reported that prior to 1949 only twenty-one cases of acute leukemia had spontaneous remissions. Birge and co-workers[3] found eleven cases from 1931 to 1949. A preliminary abstract by Diamond and Luhby[4] reported twenty-six cases of spontaneous remissions of 300 children who had acute leukemia. Others[5, 6, 7, 8] reported spontaneous remissions in a small percentage of their patients. Southam and associates[9] in summarizing the available data on possible "spontaneous remissions" indicate that few of these remissions reported elsewhere can be considered valid. Of 150 cases presented by this group, only thirteen (8.7 per cent) showed any remissions; two were complete marrow remissions (1.3 per cent). There was a total incidence of 4.0 per cent of complete or assumed remissions. In no case was there more than one single period of remission. In spite of the information provided by these reports, it should be recognized that these remissions were temporary and seldom were the remissions of as long duration as those seen with folic acid antagonist therapy.

RACE

Of the forty-eight patients in Group A, only two (4.2 per cent) were Negroes. The low incidence of Negro patients previously described by other workers is apparently borne out when one considers that the Negro population in this hospital is generally significantly higher than this percentage. Only one Negro girl was studied in Group B.

NATIONALITY

A variety of ethnic groups were presented indicating that, with the exception of Negroes, acute leukemia is found in all economic groups and in all national origins. Our data provide evidence against the commonly held belief that acute leukemia is found more often in light-complexioned people. Since the majority of our patients were drawn from areas heavily populated by dark-complexioned individuals it emphasizes that a more critical appraisal be made of population distribution in any patient survey.

AGE AND SEX

The sex distribution of the patients was of interest, since there were seventeen females and thirty-one males in Group A and eleven females and twenty-seven males in Group B. This is not in agreement with some reports which claim that more females are affected than males. It was of interest also that the distribution of males and females was in approximately the same

age group. It will be seen (Fig. 1) that the majority of the cases in both sexes occur in the preschool child. The lower incidence of cases between 8 and 11 years of age in our series is in agreement with the observations of others. While in general no strict relationship exists between the age of the patient and the severity of the disease, it should be noted that none of our infants below the age of one year survived for any prolonged period. The cases in this age group were so fulminating that we were unable to maintain adequate therapy for a long enough period to elicit a favorable response. Some children in the preschool group manifested a rapidly failing course similar to the infants. The greater incidence of this devastating disease in the preschool age group has been observed by many workers in many countries and in various economic groups, and poses many problems which may hold the key to etiology in this disease.

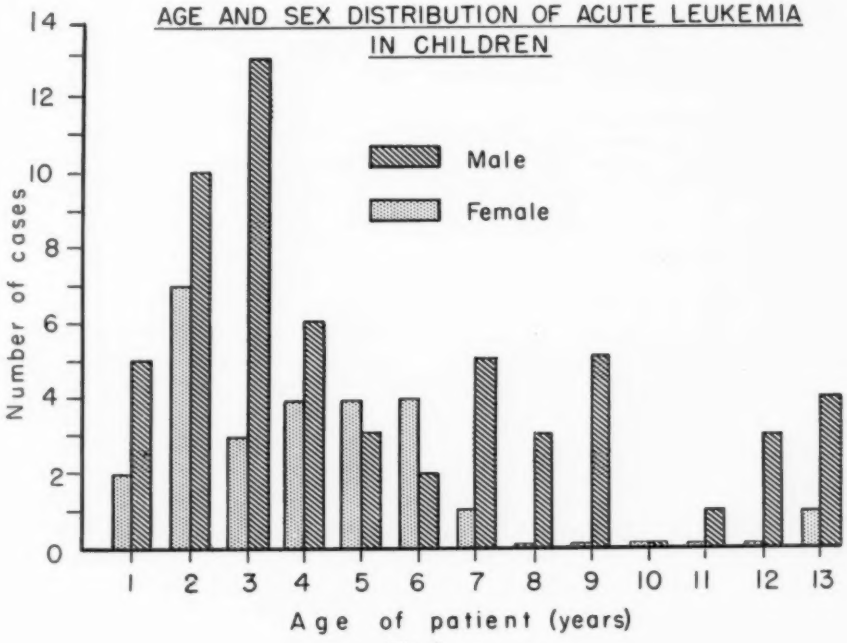

Fig. 1.

SYMPTOMS

It is difficult to assess the onset of any serious illness such as acute leukemia since one must rely upon the subjective information provided by the parents. One complaint may be prominent in one patient but not in another. A tabulation of the major symptoms reveals that increasing pallor and listlessness were noted by the parents in the majority of the cases (Table I). The symptoms and signs in the preschool child were also frequently those of upper respiratory disease, pallor, anorexia, painful extremities or lymphadenopathy. Additional complaints

included abdominal pain, increased size of the abdomen, diarrheal stools, and headaches.

An attempt to correlate age with a group of symptoms revealed no clear-cut pattern, but many of the infants manifested signs of an upper respiratory infection. These initial complaints rapidly developed into other signs and symptoms typical of the more fulminating disease process. Pallor and anorexia appeared earlier in these cases and frequently directed attention to the illness.

TABLE I. NUMBER OF CHILDREN WITH ACUTE LEUKEMIA HAVING MAJOR COMPLAINTS AT ONSET OF DISEASE

COMPLAINTS	ORDER OF COMPLAINTS		
	1ST	2ND	3RD
Listlessness and fatigue	13	10	9
Pallor	14	4	4
Upper respiratory infection	10	1	2
Fever	6	4	1
Adenopathy	10	6	3
Loss of appetite	13	4	5
Bleeding, ecchymosis, hematuria	7	8	8
Weight loss	3	3	3
Pain in extremities	10	5	2
Leukemia cutis	2	0	0
Headaches	3	2	1
Abdominal pain	2	4	4
Diarrhea, vomiting	1	2	4
Splenohepatomegaly	1	4	0
Periorbital swelling	0	1	3
Enlarged abdomen	4	3	3
Dyspnea	0	0	4

Our observations are in general agreement with the analyses of symptoms in cases reported by other workers. Differences in several reports are probably attributable to the inherent variability of the disease, the capacity of the parents to detect early symptoms, and the extent to which details were requested in history taking. It should be emphasized that the classical textbook picture of the onset of acute leukemia in children with splenic enlargement is based upon a cross-sectional study of patients and does not represent the early clinical picture of the disease in any individual case.

DIAGNOSIS FROM PERIPHERAL SMEAR

Since early laboratory verification of the disease is desirable, we were interested in the number of patients in whom the diagnosis could be established from the peripheral smear. Thirty-four of the forty-eight cases in Group A showed abnormal cells in their peripheral smear, thus calling attention to the child's probable diagnosis. The remainder were not diagnosed by peripheral smear and two had bone marrow aspirations later, thus proving the diagnosis. Instances in which the peripheral blood does not contain "blast" cells have been observed occasionally by many workers. Since "blast" forms may be mistaken for lymphocytes, the laboratory report submitted to the physician often makes no mention of abnormal forms. If unusual cell types are noted, and if the patient has lymphadenopathy, a mistaken diagnosis of infectious mononucleosis may be made. Any doubt concerning the validity of the diagnosis renders a bone marrow aspiration imperative, since typical changes may be observed in the marrow long before abnormal cells appear in the peripheral blood. The site of marrow puncture, in contrast to what has been stated in some reports, has no bearing on the accuracy of diagnosis, since the entire marrow is involved. The incidence of cases diagnosed from the peripheral smear in patients from Group B was not remarkably different from those of Group A.

EXTRAMEDULLARY LEUKOPOIESIS AND INFILTRATION

It is necessary to define metastasis in this instance since acute leukemia

as such does not "spread" to any tissue. It is fundamentally an involvement of the bone marrow, but the lymphatic tissues are affected by the same dysplastic process. Thus, a patient having complete involvement of the bone marrow and much lymphadenopathy with hepatosplenomegaly may manifest leukemic infiltrations of the bone which are not metastases. Our observations that the bone lesions demonstrable by x-ray improve under Aminopterin therapy is in agreement with other workers.[10, 11] The bone pain is relieved only after prolonged antagonist therapy, and the limp, which frequently persists for weeks or months, improves as the remission is maintained in the patient. One of our patients, in his third year of remission, had a persistent limp in spite of the improved x-ray appearance of the skeletal lesion. Bone pain was not usually completely relieved by salicylate or codeine administration. Persistent bone pain frequently interfered with the patient's appetite and well-being. Several patients had leukemia cutis, exemplified by erythematous, ecchymotic, indurated, and infiltrated raised areas. Terminally, many patients had ecchymoses and petechiae.

The hyperpigmentation of the skin seen in patients receiving Aminopterin has been previously reported by us.[12] The majority of our cases that came to autopsy provided skin specimens that are under histological study with special staining techniques to provide further data on the melanogenesis observed in patients treated with folic acid antagonists. Hyperpigmentation has been striking both in patients who have responded to the antagonists and in those who have not had a remission but who have survived for prolonged periods. Up to the present time experiments dealing with the role of the adrenal gland melanin precursors and folic acid antagonists in the production of skin hyperpigmentation have not provided an explanation for the phenomenon.

BLEEDING TENDENCIES

A variety of hemorrhagic manifestations occurred in many of the patients during the course of the disease; all showed some type of bleeding in the terminal stages of the disease. Ecchymotic areas over bony prominences were frequently seen late in the disease. Epistaxis was a common manifestation, and nasal packs were often required to halt the constant blood loss. Oozing of blood from mucous membranes in the mouth and lower intestinal tract was frequently observed and was found to be an early sign of thrombocytopenia. Many agents such as topical thrombin gauze or Gelfoam were used to diminish the bleeding but in many cases such therapy was without avail. Our experiences with toluidine blue administration for counteracting hemorrhage are of interest. The compound was administered intravenously to several patients with hemorrhage in dosages varying from 5 to 20 mg. per pound of body weight, but no beneficial results were observed. This is in contrast to the favorable results reported by others.[13]

At the present time no completely adequate explanation is available for the bleeding that occurs in the terminal phase of this disease. In all probability a combination of factors serves to produce the "hemorrhagic tendency" which is so commonly seen in the late stages of the disease. Platelets may be markedly diminished or absent from the blood (as is frequently observed when the disease runs its natu-

ral course), vascular wall weakness may exist, and an increase in some heparin-like substance responsible for prolonged coagulation of blood may all contribute to the terminal bleeding. Freeman and Hyde[14] found that bleeding rarely occurred in the leukemia cases they studied unless the circulating platelet count was below 50,000. However, they point out that the changes in the permeability of the vascular tree in leukemia undoubtedly also contribute to the extravasation of blood. These workers also concluded that "bleeding occurred with equal frequency among those with normal and those with elevated heparin-protamine titers." The toxic effects of folic acid antagonists also contribute to the hemorrhagic diathesis, thus rendering it even more difficult to study the primary mechanism responsible for hemorrhage.

NEUROLOGICAL OBSERVATIONS

Some intriguing symptoms observed in several of the cases were those that were apparently the result of central nervous involvement. In some cases, as the child began to fail, comalike episodes were noted in which the child did not respond to any stimulus. The symptoms were clinically those of intracranial bleeding, and without exception no bleeding was found within the brain or meninges to account for the symptomatology. One child, K. S., who lived for twenty-two months with folic acid antagonist therapy, developed hydrocephalus, internal strabismus, McEwen's sign, and difficulty in vision for two months prior to his death. At autopsy, no evidence of any block in the circulation of cerebrospinal fluid was found that could explain the hydrocephalus.

ROLE OF TRANSFUSIONS

The therapeutic role of transfusions can be established only after critical evaluation in cases before and after antagonist therapy. Fresh whole blood was given to all patients in both Groups A and B only when clinical judgment deemed it necessary and when actual hemorrhage or capillary oozing indicated the absence of effective hemostasis. It was our opinion that blood transfusions which were given at intervals during continuous antagonist therapy served in a supportive way and did not appear to influence the disorder or the metabolic process in specific manner.

Bierman and his group[15] felt that a combination of transfusions and antibiotics gave greater survival times than transfusions alone. However, their data also provided the conflicting evidence that the group treated with transfusions and antibiotics but with irradiation or radiophosphorus in addition survived only 5.8 months. They concluded that while transfusions alone were not able to prolong life, the addition of penicillin and sulfonamides did give increased survival time. This survival time is not significantly different from that observed by other workers in untreated patients.

The important issue here is that transfusions in all probability provided our patients with the hemoglobin, white blood cells and platelets which enabled them to withstand the disease and the therapy more effectively. It has been postulated by Sabin and collaborators[16] and by Schwind[17] and confirmed by Ross and Schoemperlen[18] that some factor in plasma aids in the maturation of the "myeloblasts" but the effect is transient and probably has little clinical significance.

MARROW SITES

It must be stressed that in observing patients treated with folic acid antagonists, frequent observation of the bone marrow is essential to proper management. Changes observed in the bone marrow are useful in altering the dosage of the drug or in determining shifts in therapy from Aminopterin to A-methopterin. The significance and need of serial bone marrow aspirations have been stressed by Smith and Bell.[19] In some cases the use of Aminopterin decreased the number of "blast" cells in the marrow to a point where they did not appear in the peripheral blood. In many cases the peripheral blood was devoid of or showed only an occasional blast cell when the marrow was still filled with the dysplastic cells. Several of the cases that relapsed began to show blast forms in the peripheral blood and this was usually interpreted as an indication for more intensive antagonist therapy. In spite of the disappearance of abnormal forms from the peripheral blood and clinical improvement in the child, marrow aspirations often indicated that the disease process was still extant. In spite of bimonthly bone marrow aspirations no difficulty was experienced when alternate bone marrow sites were used to obtain representative cellular material for microscopic evaluation.

INFLUENCE OF INFECTIONS AND LEUKOCYTOSIS

It has been observed that when an infection occurs in a child with acute leukemia the ability to withstand that infection depends upon several factors. If the peripheral white count is between 25,000 and 50,000 or higher the infectious process itself may be thought to exert a beneficial effect in that the count is reduced. It is of interest that in those patients with white blood cell counts of 25,000 or over, the ability to withstand infection was no better than in those patients who had leukopenia. This can be explained by the fact that the immature cells are probably incapable of adequate phagocytic function and thus cannot satisfactorily aid in overcoming the infectious agent. For this reason, antibiotic therapy was readily instituted with any sign of an infectious process, regardless of whether the white blood cell count was low or high.

The patients in Group A treated prior to 1948 received a variety of therapeutic measures, none of whom was helpful in resisting or overcoming infection. The patients in Group B, who were studied in the past three and one-half years, varied in their ability to withstand infection. The patient who has now survived nearly three years had a draining anorectal abscess on admission. Aminopterin was administered for three weeks together with vigorous antibiotic therapy, and the abscess healed. Patients who had mastoiditis, tonsillitis, and/or otitis media were frequently helped by the administration of an antibiotic but no influence on the leukemic process was noted.

The course of antibiotic therapy was never prolonged beyond the need of overcoming the acute infection. This point is of interest since experimental work done in this laboratory[20] has indicated that when aureomycin is fed or injected into rats receiving Aminopterin in the diet, the antibiotic is able to overcome the growth-depressing action of the antagonist by altering the intestinal flora so that the latter synthesize folic acid and/or citrovorum

factor available to the rat. The question naturally arises whether prolonged aureomycin therapy will nullify the effect of the folic acid antagonist in patients. While the data are not complete, we feel that the observations in rats are not paralleled in the patient and that Aminopterin remains effective in spite of the use of aureomycin.

Zuelzer[21] has attempted to correlate the degree of leukocytosis with prognosis in acute leukemia. He indicated that the higher the white blood cell count the poorer the prognosis. Southam and associates[9] have found a similar correlation. In partial confirmation of these observations we have had five patients with white counts of 100,000 to 600,000 and with marked lymphadenopathy and massive hepatosplenomegaly in whom the course of disease was fulminating. These high white counts are probably manifestations of ectopic leukopoiesis. Two of these patients, however, responded remarkably to Aminopterin as demonstrated by a drop of white count to normal and resolution of lymphadenopathy and splenic enlargement to approximately normal size. In general, where the process is limited largely to the bone marrow the opportunity for the antagonist to function most effectively is probably better.

LENGTH OF TIME FROM FIRST SYMPTOMS TO DIAGNOSIS

It is frequently difficult to fix the exact time of onset of any disease, and a critical evaluation of the patients' histories may not give reliable data since the informant may have provided inaccurate observations. With this point in mind the data in Table II of this "period of diagnosis" must merely be considered as an indication of the variability of the course of the disease. The diagnosis was made by the referring physician or by us shortly after admission and a real attempt was made to ascertain the exact time from the onset to the diagnosis.

TABLE II. LENGTH OF TIME FROM FIRST SYMPTOM TO DIAGNOSIS

	AVERAGE IN MONTHS	RANGE
Pre-Aminopterin (Group A)		
31 Males	3¾	2 to 7 mo.
17 Females	4	10 da. to 5 mo.
Post-Aminopterin (Group B)		
27 Males	2	2 wk. to 5 mo.
11 Females	2	10 da. to 5 mo.

It is interesting that the over-all average for the seventeen females was nearly the same as that of the thirty-one males in Group A and likewise in Group B. However, scrutiny of the individual figures exclusive of the widest range reveals that the diagnosis was made in the majority of the cases from one month to six weeks after what was presumed to be the initial symptom.

DURATION OF ILLNESS

The eighty-six case histories in both groups were carefully screened in order to determine the total duration of the illness from the first day of onset to the day of death. It should be understood that the histories may have been inadequately obtained, and that the first day of onset is not definitive. However, a rather good approximation can be made by careful questioning of the parents. Of the total cases reviewed, fifty-six were considered as reliable sources of information. The scattergram in Fig. 2 shows that no strict correlation can be made between the age of the patient and the time that the patient will survive. There is a suggestion from the data (Table III) that the average untreated patient does

not live beyond five and one-half months. The majority of children do not survive for more than four months.

The duration of illness can be considered identical with "duration of life" or "survival time" reported by other investigators since the disease is usually fatal. Since an upper respiratory disease may precede the diagnosis of acute leukemia, the duration of this "prodrome" will also affect the determination as to the start of the dysplastic process. For example, our data coincide with those of Southam and his group[9] in which the upper respiratory infection so often appears as an early symptom, but other workers, Cooke,[22] Pierce,[23] and Warren,[24] have considered these as incidental infections.

TABLE III. DURATION OF LIFE AFTER INITIAL SYMPTOMS IN PATIENTS WHO EXPIRED (AS OF FEB. 1, 1952)

	PREANTAGONIST CASES GROUP A	ANTAGONIST-TREATED CASES GROUP B
Male	5.5 (18)	11.2 (14)
Female	5.2 (7)	7.1 (4)
	Mean 5.45 mo. (22.9 wk.)	Mean 13.3 mo. (18) (42 wk.)

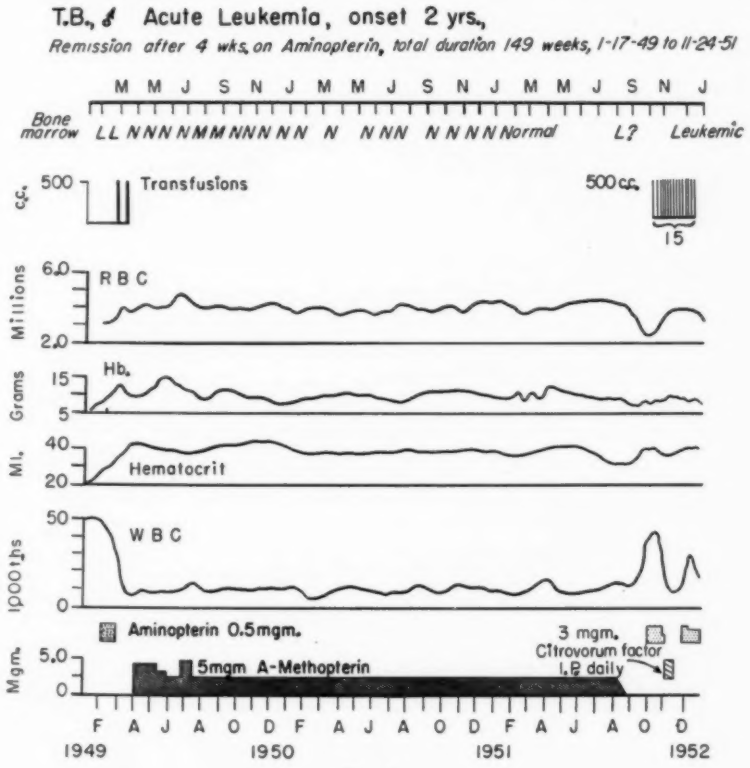
T.B., ♂ Acute Leukemia, onset 2 yrs.,
Remission after 4 wks. on Aminopterin, total duration 149 weeks, 1-17-49 to 11-24-51
M M J S N J M M J S N J M M J S N J
Bone marrow
L L N N N N M M N N N N N N N N N Normal L? Leukemic
c.c. 500
Transfusions
500 cc.
15
Millions 6.0 2.0 RBC
Grams 15 5 Hb.
Ml. 40 20 Hematocrit
1000 cts 50 0 WBC
Aminopterin 0.5mgm.
3 mgm. Citrovorum factor I.P. daily
Mgm. 5.0 0 5mgm A-Methopterin
F A J A O D F A J A O D F A J A O D
1949 1950 1951 1952

Fig. 2.

ADMINISTRATION AND PROGRAM OF THERAPY OF FOLIC ACID ANTAGONISTS*

Once the diagnosis of acute leukemia was established and after base-line

*We are indebted to Dr. J. M. Ruegsegger, Lederle Laboratories, Inc., for supplying the folic acid antagonists.

metabolic studies were made on blood and urine for several days Aminopterin was started by administering 1 mg. parenterally for two days. Oral medication was then started at 0.5 mg. dosage once daily. This was continued for as long as necessary to permit a remission in the marrow or until a change to the less toxic (but less effective) A-methopterin was deemed advisable. Our patients were given the same dosage regardless of age and body weight, although between 25 and 50 μg per kilo body weight have sometimes been suggested as a guide to dosage. We have found great tolerance to Aminopterin in some patients with leukemia since no signs of toxicity were seen after prolonged therapy in some cases for as long as six to eight months. Bone marrow aspirations were done at biweekly intervals until a remission occurred, and at monthly intervals thereafter. Complete blood counts were done at three-day intervals for the first six weeks and at intervals indicated by the clinical course of the patient but no less than at weekly intervals. A-methopterin was prescribed in 5 mg. dosages, but a few patients received 2.5 mg. for prolonged periods following their remission. This latter level is presumably inadequate since two of our patients have slowly relapsed after being in remission for one to two years. It seems necessary to provide at least 5 mg. of A-methopterin for continued effect on the bone marrow.

EFFECT OF ANTAGONISTS ON TIME OF BONE MARROW CONVERSION

Since the duration of the disease had been determined in the pre-antagonist Group A, we can compare the length of survival in the patients in Group B who received Aminopterin. Farber and his group[25] have arbitrarily chosen three weeks as the minimum time of antagonist therapy in which a therapeutic response could be expected. Although this group felt that if a patient did not respond in three weeks he would not respond at all, our experience has indicated that some children will respond only after a more lengthy course of Aminopterin therapy. Table IV provides data bearing directly on this point. It will be seen that of these patients who showed a bone marrow remission most of them converted to a normal marrow between 5 and 15 weeks. The mean was 8.9 weeks and the median was between 5 and 6 weeks.

TABLE IV. DURATION OF AMINOPTERIN THERAPY BEFORE BONE MARROW CONVERSION

	IN WEEKS
K. C. o	7
H. K. o	2
B. M. x	6
D. B. x	5
T. B. x	6
F. H. x	15
K. S. x	7
J. B. x	12
J. R. x	3
L. C. o	5
C. L. x	12
B. R. x	8
12 patients	Median – 5.0 + 6.0
	Mean – 8.9

o = female; x = male.

The data provide the basis for our recommendation that antagonist therapy should be continued throughout the duration of the disease under carefully controlled conditions. Careful laboratory observation must be accompanied by adequate medical supervision. Although bone marrow conversion is the desirable objective of any therapy, the improved clinical status

and the prolongation of life obtained with Aminopterin in some patients, in spite of a lack of bone marrow response, may be observed.

TABLE V. TOTAL DURATION OF BONE MARROW REMISSION IN ACUTE LEUKEMIC PATIENTS AS OF FEB. 1, 1951

		IN MONTHS
B. M. x		6½
D. B. x		3
T. B. x		34
F. H. x		20
K. S. x		20
J. B. x		5½
J. R. x		1
L. C. o		2½
C. L. x		4½
B. R. x		8
K. C. o		6
H. K. o		2
12 patients	Median	– 5½-6 mo.
	Mean	– 9.4 mo.

x = male; o = female.

marrow remission persisted for an average of 9.4 months in twelve patients. It must be stressed that this is an average figure and includes two patients who have only recently had a remission, and three patients who have had a lengthy remission. Seven of the twelve patients have had a bone remission for a period greater than the mean total life expectancy listed in Table III.

Table VI presents additional interesting information only on those patients who showed the bone marrow remission including the two patients who recently had bone marrow conversions. It will be seen that the mean duration of illness was 15 months; and

TABLE VI. ACUTE LEUKEMIA IN PATIENTS WITH REMISSION AS OF FEB. 1, 1952

PATIENT	TOTAL DURATION OF ILLNESS (MO.)	TIME ELAPSED BEFORE THERAPY (MO.)	TOTAL DURATION OF THERAPY (MO.)
B. M. x	13	2	10
D. B. x	6	1	5
T. B. x	35	¼	34½
F. H. x	29	1½	22½
K. S. x	22	2	20
J. B. x	15	4½	11
J. R. x	7	2	5
L. C. o	4	1	3
C. L. x	15	8	7
B. R. x	12	1	11
H. K. o	12	2	7
K. C. o	9	1¾	7¼
Median	12 + 15	1.5 + 2.0	7 + 10
Mean	15.0	2.25	11.9

x = male; o = female.

DURATION OF BONE MARROW REMISSION

The average survival time of antagonist-treated patients must be differentiated from duration of bone marrow remission. The former will be longer, depending upon how soon after the onset of the disease therapy was instituted and often reflects clinical improvement before bone marrow conversion. Table V presents data to indicate that the actual period of bone

the total duration of therapy was 11.9 months. The difference between these two figures approximates the time that elapsed in these patients before therapy was begun. Considering that delay in diagnosis and the resultant lapse of time prior to initiation of therapy prejudiced the probability of response to the metabolic antagonist, it is gratifying that our remissions were as successful as they were.

EFFECT OF AMINOPTERIN ON DURATION OF ILLNESS

Table III provides data consistent with the interpretation that Aminopterin is able to prolong life. The increased duration of life was accompanied by clinical improvement in some cases, in spite of failure of the bone marrow to convert to a more normal picture. The data are not weighted by several patients who were in long remission since many of the patients in the antagonist-treated group were included although no bone marrow conversion was observed. The table also indicates that the prolongation of life in the antagonist-treated group is statistically significant. The longer duration of life noted in the males is probably not truly limited to this sex since the majority of our patients were males.

While it would appear that Aminopterin and A-methopterin are able to prolong life in many cases if carefully administered, it is difficult to forecast the exact prolongation of life that Aminopterin can provide because of the variable clinical picture when the child is first seen. It was our impression that, if the medication was begun early in the disease, it was possible to effect a more favorable response. However, in some children who had signs and symptoms of a more advanced process a beneficial therapeutic result could sometimes be obtained. In several cases, the poor state of nutrition, the severe anemia, and the advance of the dysplastic bone marrow seemed too great a hurdle for the metabolic antagonist to overcome. In spite of these clinical obstacles, the beneficial results in some cases were encouraging enough to warrant further use of these compounds.

Fig. 2 illustrates a condensation of the data from a 5-year-old boy who had been observed for nearly three years. His bone marrow converted to normal after six weeks of 0.5 mg. Aminopterin therapy and remained in remission for a period of thirty months. He was temporarily lost from our supervision, and relapsed after being maintained on 2.5 mg. A-methopterin for months. After Aminopterin was reinstituted at the 0.5 mg. level, he was apparently more sensitive to this dosage since mucosal lesions appeared more readily than previously.

ROLE OF CITROVORUM FACTOR IN MOUTH LESIONS AND BLEEDING

The patients who showed mouth and buccal mucosa lesions following folic acid antagonist therapy probably received slight overdosages of the drug. The lesions appeared at varying times after the initiation of therapy but were consistently found on the buccal mucosa adjacent to the occlusal surface of the molar teeth. The lesions were sometimes seen at the base of the faucial pillars and on the soft and hard palates, as well as adjacent to the gingival areas of the lips. When closely observed, each lesion was seen to start as a pin-point hemorrhage that grew to an erythematous area, then formed a grayish-white membrane resembling an aphthous ulcer surrounded by edematous tissue. These lesions were painful and often interfered with the patient's food intake. It seemed that if the lesion was caused by a folic acid antagonist, then folic acid, or better still, citrovorum factor[26] injections, would cause healing of the lesions. We have now treated eight patients with severe buccal mucosa lesions with 3 mg.

of citrovorum factor (Leukovorin*). The ulcerous lesions responded in from three to six days and appeared much improved in spite of continued Aminopterin administration. When the lesions disappeared, citrovorum factor was discontinued since it seemed unreasonable to provide, for longer than necessary, one of the substances that Aminopterin was antagonizing. Several episodes of mouth lesions in a number of patients have responded successfully to 3 mg. citrovorum factor daily. We feel that citrovorum factor promotes healing of the mucosal lesions and we have reason to believe from occult blood tests on stools that enteric mucosal lesions responded also.

Our clinical observations have provided some evidence that administration of citrovorum factor alone may actually intensify the leukemic process. This is not unexpected if it is agreed that the antagonists are citrovorum factor antagonists as well as folic acid antagonists. We have found that administration of 3 mg. of citrovorum factor daily to a newly diagnosed acute leukemia was associated with still greater lymphadenopathy. This therapy was given for a three-week period to a 2½-year-old girl but was discontinued when the lymph nodes remained enlarged. In other cases in which citrovorum factor was given to counteract the buccal mucosa lesions, we have observed increased splenomegaly within a five-day period. It seems, from these few observations, that administration of citrovorum factor is hazardous unless nearly stoichiometric amounts of Aminopterin are given simultaneously to "neutralize" the action of citrovorum factor. It has been shown in animal experiments that as more citrovorum factor is added to the diet, increasing amounts of Aminopterin can be given.

*Supplied by Lederle Laboratories, American Cyanamid Division, through the courtesy of Dr. J. M. Ruegsegger.

DISCUSSION

The use of folic acid antagonists by Farber and his group[1, 27] first demonstrated that temporary remissions could be obtained in a disease which heretofore was not significantly affected by arsenicals, radioactive phosphorus, and x-irradiation. The responses to Aminopterin and A-methopterin obtained in our series of cases were more favorable than those observed prior to the use of the antagonists.

Any comparison of the total duration of life in untreated patients with those given antagonist therapy must take into consideration several factors:

1. Are diagnoses of acute leukemia in children made more readily today than twenty years ago? It may be that the increasing awareness of the significance of bone marrow aspiration in children by some physicians has helped diagnose some cases earlier, but the majority of patients seen in this hospital during the past twenty years were subjected to bone marrow aspirations. We feel therefore that antagonist-treated patients were not diagnosed any earlier than the pre-antagonist cases and that the interval between onset of the disease and appearance at this hospital remained the same in the two groups studied. Table VI lists the average time elapsed from the onset of the disease (as determined by history) to the beginning of therapy as about two months. This finding was observed both in Groups A and B.

2. Does the apparently increased duration of life really represent a longer period of observation by us be-

cause the diagnosis was made earlier? While the number of cases observed by us is not large, thirteen of fifty-two patients were untreated or received some therapy for less than three weeks (Table VII). Of these, four received no therapy of any kind. The mean survival of the thirteen cases was 2.8 months ranging from one to six months, and the mean of the four cases was 1.5 months. When these means are compared to the mean survival of the cases in Group A, one obtains evidence that patients do not survive longer than did patients twenty years ago, nor does an earlier diagnosis account for the longer survival time of patients treated with folic acid antagonists.

TABLE VII. SURVIVAL TIME IN PATIENTS RECEIVING NO AMINOPTERIN OR INCOMPLETE COURSE OF THERAPY

PATIENT	SEX	AGE (YR.)	THERAPY	MONTHS
E. B.	M	2½	19 da. Aminopterin	2½
J. S.	M	3	19 da. Aminopterin	1½
H. E.	M	9	7 da. Aminopterin	6
E. W.	M	7	----------	1
G. P.	M	5	3 da. Urethane 8 da. Aminopterin	4
B. T.	F	2	19 da. Aminopterin	4
L. D.	M	6	----------	2
W. S.	M	½	2 da. Aminopterin	1
W. F.	M	⅔	3 da. Nitrogen Mustard	3
C. H.	F	4½	5 da. Aminopterin	
P. M.	M	1	----------	1
L. G.	M	7	8 da. Aminopterin	3
B. C.	F	2½	----------	2
			Average	2.8

We emphasize that these compounds can in no way cure the disease, but their effects offer an approach to the study of basic mechanisms involved in the disordered cellular pattern characteristic of acute leukemia. This discussion will deal with these mechanisms primarily as they can be defined from the clinical results.

One interesting feature of therapy of leukemia with the folic acid antagonists is the marked clinical improvement which occurs in some cases in spite of the lack of bone marrow remission. This has also been observed by Farber and his group.[25, 27] This improvement can be judged best by the improvement in appetite, the decrease in fever, abdominal pain, bone pain, and in the size of the spleen, liver, and lymph nodes. Approximately half of the patients who did not show bone marrow conversion after being treated for more than three weeks did show some clinical improvement. Since the antagonists are able to cause a decrease in the size of the spleen and liver, there is often accompanying relief from abdominal pain. Experience indicates that antagonist therapy must be continued for some time before a cellular response occurs.

The total number of patients treated with Aminopterin was thirty-two; twenty-five were boys and seven were girls. Zuelzer[21] and others have found a higher incidence in girls rather than boys. We have no explanation for this discrepancy. The age at onset of the disease seemed to be from 2 months to 13 years. The median age for both sexes is 3½ years, but the mean age is 4¼ years. Because more boys than

girls were treated with the antagonists more remissions were obtained in the boys, but no significant difference in percentage responses was noted in either sex. It is of interest in this connection that Goldin and co-workers[28] found that mature male mice were uniformly more susceptible to the effects of the antagonists than female mice, but in immature mice the sex differences were not apparent.

Our experience during the past three and one-half years has furthered our impression that a variable period of time is necessary before Aminopterin therapy can cause remission of the abnormal marrow if it will occur at all. The patients usually responded in two to fifteen weeks after antagonist therapy was begun. Several patients never showed a change from the "blastic marrow" in spite of intensive therapy over a long period of months. We believe this to be significant since the symptomatic care of these patients was not basically improved over the pretreatment group. Antibacterial drug therapy did not seem to influence the clinical course sufficiently in the antagonist-treated group. This confirms the experience of Bierman and associates.[15] Fortunately, when therapy is begun early and given intensively, the process is so altered that the bone marrow can produce apparently normal red and white cells.

Some patients receiving antagonist therapy appeared to be getting worse, but with continued administration of the drug they were able to survive this critical period and proceeded to show a definite clinical improvement, sometimes followed by bone marrow remission. The agranulocytosis that has been found to accompany clinical deterioration may be followed by marked subjective improvement. This has been observed in six of our cases so that the patient appeared worse before he showed improvement. One striking example was a patient, T. W., who was leukopenic for several weeks and who was supported by blood transfusions and antibiotics and who had a remission four weeks after this critical period in which his condition was deemed terminal. Bassen and Kohn[8] reviewed previous findings and reported a similar observation since their patient had an agranulocytic phase prior to the several bone marrow remissions. At present no adequate explanation for this observation can be given.

It is of interest to speculate on the reason for the variable individual responses to Aminopterin or A-methopterin. The response appears to be unrelated to the age or sex of the patient. Apparently the longer the disease exists prior to treatment, the less favorable the response. The effectiveness of the antagonists was decreased in successive relapses in some patients and death inevitably resulted. The final relapse may have been due to the production of an aplastic marrow caused by the constant toxic effect of the antagonists in some cases. Bone marrow specimens obtained at autopsy indicated that this was true only in a few instances. No difficulty was encountered in obtaining material from the narrow in spite of the numerous bone marrow aspirations performed on our cases.

In the leukemic disease process the inability to produce mature cell elements is in all probability the result of metabolic aberrations in the bone marrow caused primarily by disordered nuclear protein metabolism. The blast cells presumably contain more folic

acid and/or citrovorum factor than normal leukocytes,[29] but it does not mean that an excess of folic acid causes leukemia. The relationship between folic acid and citrovorum factor has not been completely clarified, but it would appear that the latter is the more active metabolic portion of the coenzymes that are concerned in normal enzymatic processes that insure maturation of the white blood cells.

function as citrovorum factor antagonists since the latter counteracts the toxicity of Aminopterin more efficiently than folic acid.

A summary of the present information on fundamental nucleic acid metabolism and the role of the vitamins and coenzymes in that scheme is shown in Fig. 3. The antagonists act either to prevent undue accumulation of folic acid or citrovorum factor within the

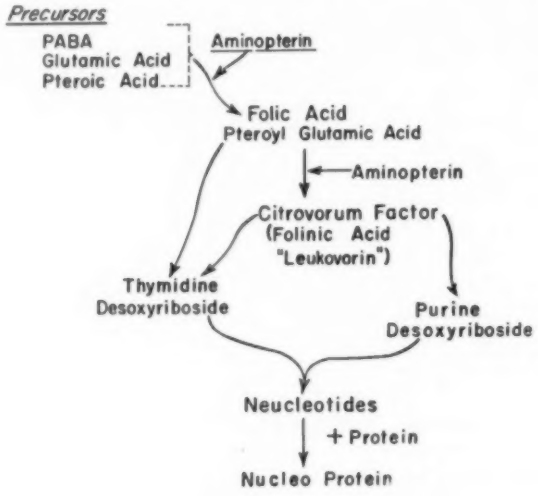

Fig. 3.

The precise mode of action of the folic acid antagonists is as yet undefined, but enough information is available to permit certain reasonable speculations. While the antagonists have been proved capable of producing a pteroylglutamic acid deficiency in most experimental animals, there is no evidence to indicate that this is the only "vitamin deficiency" produced. To state it another way, the antagonist may well antagonize related substances in addition to folic acid. Experimental evidence from our laboratory[20, 30] indicates that these antagonists also

early cell forms or to allow normal maturation processes (which act through still other enzymes) to proceed. It seems illogical to presume that the antagonists exert their beneficial action by merely interfering with folic acid alone, since it has been shown by Weber and associates[31] and by others that the administration of 20 to 30 mg. folic acid per day to acute leukemias in remission did not cause a relapse to the leukemic state. However, if no mechanism exists for converting folic acid to citrovorum factor, then giving the former will be without

effect. Further indirect evidence against the "excess folic acid" idea is apparent when one realizes the ubiquity of the vitamin in plant and animal food sources and it might therefore be anticipated that more cases of leukemia would occur.

While the coenzymes may be important in the normal maturation process of the marrow elements, the amino acid and protein fractions are also important in the formation of the enzymes proper. These enzymes are actively concerned in the formation of desoxyribosides, thymidine, and other nucleic acid precursors plus a specific protein. We may speculate that the maturing white blood cells in leukemia probably lack portions of an enzyme system or systems which enable it to assume its final morphogenetic characteristics.

Preliminary evidence from this laboratory[32] indicates that certain of the amino acids are found in greater amount in the plasma of leukemic individuals than control patients. At this point we may only speculate this to be the result of inefficient synthesis of protein, since these amino acids may circulate at higher concentrations because they are not being synthesized into definitive protein.

Despite the very favorable responses in some cases to antagonist therapy, we have no ready explanation why the effectiveness of these compounds decreases and finally fails to maintain the beneficial effects in a particular patient. The speculations that have been alluded to in the above discussion are based on clinical experience and investigation. We feel that the results reported here are not the result of mere "toxic" effects on the marrow as has been the case with other therapeutic agents as arsenicals, urethane, etc., but rather a specific influence of metabolic antagonists on disordered enzyme system concerned in cellular maturation. All these substances may have a common mode of action but with greater delineation the defect may well be found in disordered nucleoprotein metabolism within the cells or in specific enzyme systems.

SUMMARY

The natural history of eighty-six cases of acute leukemia in children has been described. Only two of these have been Negroes. Preschool age children are primarily affected and the average life expectancy is 5.5 months. The folic acid antagonists, Aminopterin and A-methopterin, have provided clinical improvement and prolonged life in the majority of cases. Bone marrow remissions have been obtained for as long as thirty months. The role of Aminopterin as a folic acid and citrovorum factor antagonist has been discussed in respect to the enzymes concerned in protein metabolism associated with cellular maturation.

We are indebted to Drs. Herbert Grossman, Robert A. Pastel, Donald Waterman, Herbert Woodcock, and Dorothy Dieter for their help in providing medical supervision of some of these patients during their tenure as residents in the department.

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EFFECT ON WEIGHT GAIN OF THE ADDITION OF LACTOBACILLUS ACIDOPHILUS TO THE FORMULA OF NEWBORN INFANTS

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IT HAS been common knowledge for many years that breast-fed infants thrive better during the first few months of life than do infants fed cow's milk formulas of the same protein level.[1, 2, 3, 4] At one time this was ascribed to the difference in the lactalbumin/casein ratio of the two milks, but more recent work has shown these two proteins to be nutritionally equivalent.[5, 6]

One of the most striking differences between the two groups is the bacterial content of their intestinal tracts and stools. The stool of the breast-fed infant is distinctly acid, and the predominating organisms are gram-positive Lactobacilli; whereas in the case of the artificially-fed infant the stool is much less acid and the gram-negative coliform-aerogenes group predominates.[2, 7, 8]

The growth of harmless lactic acid producers in the intestinal tract brings about a condition of acidity which can inhibit the growth of potentially harmful organisms. A moderate degree of acidity also promotes the absorbability of calcium salts.

The possible advantages of a gram-positive aciduric flora in the intestine and the better digestibility of acidified (sour) cow's milk for infant feeding have resulted in a voluminous literature on the use of cultured milks for both infant feeding and therapeutic purposes.[9, 10, 11] More recent work has shown that synthesis by the intestinal flora can also be a significant source of vitamins and other essential growth factors.[12, 13, 14, 15]

On the basis of these facts an exploratory experiment was devised to determine possible nutritional significance of the two types of flora.

METHODS

The experimental work was done at the Mercy and Fort Hamilton Hospitals, Hamilton, Ohio. All infants delivered in both hospitals over a six-month period were divided into four groups in the order of their birth. Each infant remained under the care of his own physician and was fed on whatever formula had been prescribed, but supplemented as follows:

Group 1 (control): No addition to the formula.

Group 2: Two milligrams of folic acid per quart added to the daily fornula.

Group 3: 500,000,000 viable *Lactobacillus acidophilus (bifidus)* organisms per quart added to the daily formula.

Group 4: Folic acid and Lactobacilli, each in amounts stated above, added to the formula.

Preparation of Culture.—The culture used was a mixture of *L. acidoph-*

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ilus A.T.C.C. Nos. 4962 and 4963 (*L. bifidus*, strains 3 and 5, L. F. Rettger). The stock culture was carried on Difco Micro-inoculum broth; transfers were made every ninety-six hours to maintain maximum activity.

The culture was prepared by adding 2 c.c. of the stock culture to 125 c.c. of Micro-inoculum broth and incubating it for forty-eight hours at 37° C. The culture was then assayed and stored in the refrigerator for use.

The folic acid was supplied by the addition of 2 c.c. of Folvite Elixer (Lederle) per quart of formula.

These additions were made to the prescribed formula only during the infants' stay in the hospital, and were discontinued at the time of dismissal. Except for premature infants, hospital stay varied from one to six days. Infants who were obviously ill in the hospital, or who had congenital irregularities, were excluded from the study.

TABLE I. AVERAGE WEIGHT GAINS DURING THE FIRST MONTH OF LIFE OF COMPLETELY BOTTLE-FED INFANTS

	NO. OF INFANTS	OUNCE GAIN	S.D.
Group 1 (Control)	123	21.9	± 9.7
Group 2 (Folic acid)	129	23.7	±10.0
Group 3 (*L. acidophilus*)	124	26.5	± 9.6
Group 4 (Folic acid and *L. acidophilus*)	134	25.2	±11.9

TABLE II. AVERAGE WEIGHT GAINS DURING THE FIRST MONTH OF LIFE OF PARTIALLY BREAST-FED INFANTS

	NO. OF INFANTS	OUNCE GAIN	S.D.
Group 1B (Control)	69	30.2	± 9.1
Group 2B (Folic acid)	83	29.2	±14.3
Group 3B (*L. acidophilus*)	79	30.7	±13.1
Group 4B (Folic acid and *L. acidophilus*)	60	30.7	±13.1

TABLE III. COMPARISON OF WEIGHT GAINS BETWEEN GROUPS

GROUPS	INCREASE (OZ.)	t (SIGNIFICANCE)*
1 vs. 2	1.8	1.44
1 vs. 3	4.6	3.74
1 vs. 4	3.3	2.38
1 vs. 1B	8.3	5.79
3 vs. 1B	3.7	2.61

*2% probability level t = 2.26.

Storage tests indicated that the culture retained its viability for at least a week, although fresh cultures were prepared every fourth day. Assay of the culture at forty-eight hours' incubation consistently showed 500,000,000 or more viable bacilli per cubic centimeter.

Inoculation of the formula was made by adding 1 c.c. of the working culture to each quart of formula. The formula was then stored in the refrigerator until used.

Weight records were kept during the hospital stay, and the weight at one month was ascertained by a follow-up letter to the mothers. Physicians' records were checked of all infants who did not gain at least 16 ounces during the first month, and those found to have been ill were excluded from the study. Approximately 1,400 babies were involved, from the mothers of whom 975 replies were received. From these about 800 acceptable weight records were obtained.

RESULTS

Stool smears on a selected group of infants after four to five days showed implantation of gram-positive rods in the intestinal tract of infants fed *L. acidophilus,* while a gram-negative flora predominated in the controls and in Group 2. Additional smears on this group at one month of age showed that the gram-positive flora persisted in the infants receiving the culture supplement, provided they remained on a predominately milk diet.

It was found very early that babies who were nursed, even for only one or two days, showed a remarkable gain in weight over those who were completely bottle fed, particularly in the control group. Following this observation the infants under observation were further divided into two subgroups: infants partially breast fed and those completely bottle fed.

DISCUSSION

The inaccuracies inherent in obtaining data of the infants' weights from the mothers are recognized, and the possible variables resulting from the use of infants from two different hospitals and from the use of a variety of formulas must also be considered. On the other hand, each of the subgroups was subjected to the same test factors and it could be expected that the variables would be so distributed among the various subgroups that the pattern of any particular group would not be affected by them.

In view of the shortcomings of the experimental setup, this study and the conclusions drawn therefrom should not be considered as conclusive evidence, but only as indicating the need for further evaluation of the relation of the intestinal flora to the nurition of the artificially fed infants.

SUMMARY AND CONCLUSIONS

Approximately 800 babies in two hospitals were fed formulas supplemented with folic acid and/or a *L. acidophilus* culture; their gains in weight were measured at the end of one month.

It was concluded that, under the experimental conditions described,

1. Infants partially nursed, even for two or three days, showed significantly greater gains in weight during the first month than did infants completely bottle fed.

2. Bottle-fed infants on formulas supplemented with *L. acidophilus* showed significantly larger gains in weight during the first month than did the controls. The gains in weight approached, but did not equal, the gains of partially nursed infants.

3. The addition of 2 mg. of folic acid per quart of formula had no significant effect on the gain in weight of either bottle-fed or partially breast-fed infants.

4. The addition of *L. acidophilus* to the formula had no effect on the gain in weight of partially breast-fed infants.

5. There appears to be an unknown factor or factors present in colostrum which causes increased gain in weight during the first month of life. A considerable part of this increase can be obtained by supplementing the formula of the completely bottle-fed infant with *L. acidophilus* for the first few days of life.

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STAPHYLOCOCCUS AUREUS INFECTIONS IN THE NEWBORN INFANT

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OUTBREAKS of pustular dermatitis among newborn infants have long been a serious problem,[1] owing to the incidence of serious complications. Prior to the use of chemotherapy and antibiotics, the mortality rate among infants with severe staphylococcic infections, i.e., pneumonia and septicemia, was reported as ranging between 50 and 100 per cent.[2, 3] Since specific therapy has become a fact, the reported mortality rates have diminished substantially. During the newborn period, however, considerable morbidity and mortality may still occur. The age and weight of the infected infants and the sensitivity of the etiological agent to treatment are vital factors determining the seriousness of any single epidemic.[4] Our recent unpleasant experience with an epidemic of *Staphylococcus aureus* infections in the newborn nursery stresses the fact that danger has not been completely eliminated.

Several unusual features characterized this particular outbreak. The etiological agent was a coagulase-positive hemolytic *Staph. aureus*, which was identifiable on culture by its unusually deep orange pigmentation. In this respect, we were dealing with a "tagged" organism. Investigation of numerous other infections occurring throughout the hospital at the same time among patients and personnel revealed that the same organism was responsible. Lack of clinical response to penicillin and sulfa therapy prompted sensitivity studies of this bacterium to sulfadiazine, penicillin, streptomycin, and aureomycin. It was found to be highly resistant to all agents except aureomycin, to which it was highly sensitive in vitro. Sites of infection included skin, conjunctivae, middle ear, breast, lung, and pleura. Many of the infections were mild, and responded promptly to specific therapy. Several, however, were severe; two cases terminated fatally.

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CLINICAL MATERIAL

During a three-month period there were thirty-nine staphylococcus infections among 231 infants in the newborn nursery. The distribution of lesions is indicated in Table I.

TABLE I. DISTRIBUTION OF LESIONS

DISTRIBUTION*	NUMBER OF CASES
Pustular dermatitis	13
Deep abscess of skin	6
Purulent conjunctivitis	4
Pneumonia	4
Lung abscess	4
Breast abscess	3
Vaginitis	2
Balantitis	1
Otitis media	1
Sepsis	1
Total	39

*More than one lesion occurred in several cases.

BACTERIOLOGY AND EPIDEMIOLOGY

The department of bacteriology cultured material from all purulent lesions. A deeply pigmented coagulase-positive hemolytic *Staph. aureus* was grown from all infected cases. Routine skin cultures were done on a group of

apparently healthy newborn infants in the nursery. Of twenty-two infants examined, five had skin that was contaminated with the "tagged" organism. None of these infants developed infections.

Shortly before the outbreak of cases in the newborn nursery, the laboratory began to culture a deeply pigmented, hemolytic *Staph. aureus* from a group of postoperative wound infections on the surgical wards. This same organism was consistently grown from purulent lesions affecting fifteen hospital employees on the various hospital wards (Table II).

TABLE II. HOSPITAL PERSONNEL AFFECTED

DATE REPORTED	SITE OF LESION	DUTY
9-12-49	Axilla	Aide
9-30-49	Forearm	Nurse
10- 5-49	Finger	Nurse
10- 5-49	Eyelids	Nurse
10- 5-49	Forearm	Nurse
10-13-49	Forearm and leg	Nurse
10-17-49	Nose	Nurse
10-19-49	Forearm and feet	Nurse
10-23-49	Finger	Nurse
10-24-49	Axilla	Nurse
10-26-49	Neck	Nurse
11-17-49	Arm	Nurse
11-25-49	Fingers	Nurse
11-29-49	Finger	Nurse
12- 1-49	Leg	Nurse

Two days after the discovery of the first case of pustular dermatitis in the nursery, a nurse's aide in contact with newborn infants was discovered to have an axillary abscess which was draining pus. In addition, a great variety of purulent lesions, each of which yielded the "tagged" organism on culture, were found among the patients and personnel throughout the hospital. Nose and throat cultures were done on all hospital personnel who were in contact with the newborn nursery. Of forty-five individuals tested, fifteen were found to have positive cultures for the offending organism. They were relieved of nursery duty until their throat cultures became negative. The fact that the infection was so widespread throughout the hospital makes it impossible to determine with certainty the original source of contamination of the nursery.

CLINICAL MANIFESTATIONS

Pustular Dermatitis.—This was the most frequent lesion. It occurred in thirteen cases. Typically, the initial finding was erythema followed by pustule formation. In uncomplicated cases, the infants suffered no apparent discomfort. They were afebrile and continued to feed and react normally. The usual treatment of opening the lesions under 70 per cent alcohol plus local and parenteral penicillin therapy failed to eradicate the infection. Culture, in all cases, revealed the "tagged" hemolytic *Staph. aureus*. Prompt healing of the lesions occurred when aureomycin ointment was used. This confirmed clinically the results of sensitivity tests.

The deep skin abscesses were unusually severe. They were usually single and contained large amounts of pus. One abscess involved the right buttock, the entire lumbar area, and about one-half of the posterior chest region. All responded well to incision and drainage and aureomycin by mouth.

Balanitis and *vaginitis* occurred. These responded readily to local and oral aureomycin therapy.

A severe type of *blepharitis* and *conjunctivitis* was seen. These were characterized by profuse discharge of thick, creamy yellow pus. Indeed, one case was so severe as to cause concern, in the beginning, for the future useful-

ness of the eyes. The use of penicillin ophthalmic ointment and solution as well as 30 per cent Sodium Sulfacetamide were ineffective. Quick response was obtained in all cases, however, when aureomycin ophthalmic solution was used.

Lung Infections.—Four infants developed severe lung infections during the epidemic. Pneumonia due to a virulent *Staph. aureus* was apparently the primary lesion, followed by suppuration of a bronchopulmonary segment and acute abscess formation. Postmortem examination revealed that this was the course in the two infants who died. In the infants who survived there was a diffuse pneumonia with the subsequent appearance of a single large radiolucent area which cleared only after weeks of therapy. Pulmonary pneumatocele or bullous emphysema, lesions which also occur secondary to pneumonia, have not been definitely ruled out; however, in view of the pathologic findings in the two fatal cases, lung abscess was probably the process in all cases.

DISCUSSION

Since the general use of chemotherapeutic and antibiotic agents, the outlook for patients with staphylococcus infections has improved immeasurably. As new agents become available, therapeutic failures should become increasingly rare. There are many reports of gratifying results from the use of aureomycin in penicillin-resistant staphylococcus infections.[5, 6, 7]

In this series inadequate response to parenteral and local penicillin prompted investigation of sensitivity of the offending organism to the available therapeutic agents. It was found that the bacterium was highly resistant to penicillin and sulfa drugs, but extremely sensitive to aureomycin. Aureomycin was administered by gavage in divided doses of 40 mg. per kilogram of body weight. Three of the patients with lung infections also received streptomycin. This was done when upon rechecking the sensitivity of the organism it was found to be sensitive to streptomycin as well as aureomycin. Despite this, one of the infants died. The other two recovered and are perfectly well.

Local aureomycin therapy in the form of 3 per cent ointment was used in cases of dermatitis. It was applied liberally over the involved areas four times daily. In many cases which had not responded to local and parenteral penicillin therapy, the lesions disappeared within a twenty-four to forty-eight-hour period after aureomycin therapy was begun.

In the cases of conjunctivitis, the aureomycin ophthalmic solution, containing 5 mg. per cubic centimeter, yielded excellent results. One drop of the solution was placed in each eye every four hours.

SUMMARY

An epidemic of infections with protean manifestations caused by a virulent, highly pigmented, coagulase-positive *Staph. aureus* is presented. The organism was highly resistant to all therapeutic agents tested except aureomycin and streptomycin. The value of sensitivity tests is stressed. Aureomycin was invaluable in controlling this epidemic.

CONCLUSIONS

1. *Staph. aureus* infections may become a severe hazard in the newborn nursery.

2. The sites of involvement are varied.

3. Sensitivity tests to various antibiotics is a valuable procedure in helping to choose the most effective available therapeutic agent.

4. Aureomycin is efficient in the treatment of some penicillin-resistant staphylococcus infections.

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LOBAR EMPHYSEMA IN INFANTS AND CHILDREN

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DYSPNEA and cyanosis in the infant and young child are alarming symptoms. Knowledge of the causes of cyanosis such as pulmonary infections of various types, atelectasis, congenital heart disease, pneumothorax, central nervous system injury, and many less frequently occurring conditions has increased with each decade. It is our purpose to direct attention to yet another cause of these severe symptoms, lobar emphysema. Within the last two years we have had the opportunity to observe six cases of this unusual condition. Despite this frequency of occurrence, we found that practically nothing was commonly known of the diagnosis, etiology, pathology, and treatment of this unique type of emphysema. The preceding statements require qualification. Emphysema confined to one segment, lobe, or lung has long been recognized. Iglauer[1] as long ago as 1911 discussed this in relation to foreign body in the bronchus, and this has been probably the most frequently noted cause of regional emphysema. There are many other reports in the literature of this type of regional emphysema due to check valve obstruction of a bronchus by bronchogenic carcinoma,[2] endobronchial tumor, inflammatory tissue or inflammatory products, or by intrathoracic masses, most commonly tracheobronchial lymph nodes[3] or aortic aneurysm. All of these lesions are more likely to cause complete obstruction and resulting atelectasis, but a partial obstruction in which air is admitted to the pulmonary tissues but not allowed to exit freely is encountered appreciably often. Holinger and Andrews[4] have made a complete classification of conditions giving rise to partial or complete bronchial obstruction. Localized emphysema, the emphysematous blebs and bullae also called pneumatoceles,[5, 6, 7] is also well known. These blebs and bullae are found in the course of pneumonias, are usually symptomless, adding little to the morbidity of the primary disease. They are of clinical importance mainly in their confusion roentgenographically with pneumothorax, lung abscess, and tuberculous cavitation, and also with congenital cystic lung disease. These localized emphysematous lesions are usually caused by partial obstruction of a lobular bronchus or one or more small bronchi, accompanied by inflammatory occlusion of the pores of Cohn which normally allow interchange of gases between adjacent respiratory units within the lung. We want to make a distinction between the cases herein reported, and these other types of regional emphysema mentioned. The five cases to be reported are unusual and distinct from these other types, and were previously thought to be infrequent in occurrence, and poorly understood as to etiology, pathology, and treatment.

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CASE REPORTS

CASE 1.—C. M., a white female, was admitted to the hospital at the age of 2 months, because of wheezing respirations and cyanosis. Within the space of a few hours, three spells of this respiratory difficulty had occurred. At one month of age, two short episodes of dyspnea and cyanosis had been noted. The birth history and early development were otherwise without abnormality. On examination, the child was seen to be critically ill. Respirations were rapid with an expiratory prolongation and a faintly audible wheeze. The right chest was hyperresonant, and a few crepitant râles were heard on the left.

Fig. 1 (Case 1).—C. M., aged 2 months. The anteroposterior view shows marked emphysema of the region of the right middle lobe with atelectasis of the right upper lobe. Right middle lobe emphysema was demonstrated at operation. Deficiency of cartilage in the lobar bronchus was found.

Roentgenograms: On the anteroposterior view marked emphysema of the region of the right middle lobe with atelectasis of the right upper lobe was noted (Fig. 1). On the lateral view it is seen that the emphysema was anterior, and the atelectasis behind the heart.

Course: With oxygen the color improved. A right thoracotomy was decided upon, and on the following day, a large emphysematous right middle lobe was found at operation. This lobe occupied the entire right hemithorax, compressing both the upper and lower lobes. Right middle lobectomy was performed. The postoperative course was uneventful, and the patient was discharged without cyanosis or dyspnea. There has been no recurrence of symptoms.

Pathology: The main bronchus to the lobe had excessive infoldings of the mucosa and decrease in the cartilage grossly. Emphysema of an obstructive nature was evidently due to hypoplasia of the bronchial cartilages.

CASE 2.—R. J., a white infant, born of a normal pregnancy and delivery, began to vomit at the age of 3 weeks. The family physician observed the child to be dyspneic, and an x-ray was said to have shown partial collapse of the right lung. The child was admitted to another hospital, and oxygen therapy was given with evident good result. Two weeks after discharge from the hospital, the infant began having attacks of vomiting, cyanosis, and dyspnea brought on by feeding and crying. On examination, the anterior left chest was hyperresonant, the right chest dull to percussion. The

Fig. 2 (Case 2).—R. J., aged 2½ months. The heart and mediastinum are markedly shifted to the right. An unusually radiolucent left lung field is seen, with atelectasis of the left lower lobe, the right upper lobe, and the right lower lobe. A lobar emphysema of the left upper lobe and a persistent ductus arteriosus extending over the left main stem bronchus was found at operation.

heart was percussed to the right. Auscultation revealed bronchial breathing and fine inspiratory râles on the right.

Roentgenograms: The heart and mediastinum were markedly shifted to the right. An unusually radiolucent left lung field was seen. Atelectasis of the left lower lobe, the right upper lobe, and the right lower lobe was also diagnosed. (Fig. 2.) A bronchogram was unsuccessful in visualizing the site of bronchial obstruction.

Bronchoscopy: The trachea was deviated to the right, the left main bronchus considerably so. The left upper lobe bronchus lay almost in a straight line with the main bronchus. An attempt was made to dilate the stenotic left lower lobe bronchus.

Course: A left exploratory thoracotomy was performed. The left upper lobe was extremely emphysematous. A persistent ductus arteriosus was seen to extend over the left main bronchus and attach low on the left pulmonary artery. The ductus, on clamping and dividing, contained granulation tissue. The ends of the ductus were sutured, and a left upper lobectomy was performed though there was some doubt if it were absolutely necessary. The lower lobe could be expanded without difficulty. Postoperatively the infant had no cyanosis, and was discharged in good health on the twelfth postoperative day.

Pathology: The tissue of the left upper lobe, except for the lingula, was very emphysematous, with numerous large bullae. In some areas focal atelectasis due to expansion of neighboring alveoli was seen. The lingula was atelectatic. Edema and early pneumonia were also present.

Case 3.—P. G., had a normal birth and early development. At the age of 6½ months he had an attack of pneumonia, followed by another episode of pneumonia three weeks later. A roentgenogram at that time showed a marked mediastinal shift. The child became cyanotic on crying even though the pneumonia was thought to have responded to penicillin. On admission to the hospital, physical examination revealed hyperresonance and diminished breath sounds over the left lung field, particularly the upper portion. The apex beat was in the midline, and the heart was percussed to the right of the sternum.

Roentgenograms: A radiolucent left upper lung field was seen to extend past the midline. The heart and mediastinum was shifted to the right. The lower half of the left lung field was minimally compressed. (Fig. 3.)

Fig. 3 (Case 3).—P. G., aged 7 months, was seen to have a radiolucent left upper lung field extending past the midline, with a shift of the heart and mediastinum to the right. The lower half of the left lung field was minimally compressed. At operation, a lobar emphysema of the left upper lobe, a persistent ductus arteriosus extending across the left main stem bronchus, and an anomaly of the pulmonary artery and the bronchi were found.

Fluoroscopic examination was not suggestive of congenital heart disease. Bronchograms showed the left main stem bronchus to be about one-third less in diameter than the right. The left upper lobe bronchus did not fill with oil.

Bronchoscopy: The trachea was deviated posteriorly, and far to the right. Considerable compression of both bronchi was noted.

Course: With the preoperative diagnosis of obstructive emphysema of the left upper lobe, a left thoracotomy was performed. Dissection around the left hilum revealed a ductus ar-

teriosus 4 mm. in diameter and 1 cm. in length, hard and fibrous, extending over the outer surface of the left main bronchus. The ductus was doubly transfixed, and severed. It was not patent. The temptation to do nothing further was resisted, and a left upper lobectomy was performed. The pulmonary artery as one branch went to the lower lobe, and then seven small branches traveled from there to the upper lobe. Likewise the bronchus went to the lower lobe before three small bronchi were given off to the upper lobe. The postoperative course was uneventful and the patient was discharged on the tenth postoperative day.

Pathology: The lung parenchyma was markedly emphysematous, that is, numerous alveolar walls were ruptured and the alveolar spaces were coalesced to form large cystic spaces. The bronchi and bronchioles showed no unusual changes. A few areas of focal-acquired atelectasis and a few intraalveolar hemorrhages were present.

CASE 4.—C. F., a 17-day-old infant, had a normal birth, though the delivery was long and thought to be four weeks past due. On the second week of life, the child had two dusky spells but the physician could find nothing to account for this. On the day of admission to the hospital, the infant had become dyspneic and cyanotic. Examination revealed irregular respirations with markedly depressed breath sounds on the right. Circumoral cyanosis was present even while the child was in oxygen. The temperature was not elevated.

Roentgenograms: The upper two-thirds of the right lung was radiolucent while the lower third was almost completely opaque. The heart and mediastinum were shifted to the left. (Fig. 4.)

Bronchoscopy: The right main bronchus was somewhat compressed. The right upper lobe orifice was depressed inferiorly from above. Two further bronchoscopies demonstrated a patent right upper lobe bronchus.

Course: Aureomycin and penicillin were begun, and the child was kept in the oxygen tent. With the thought that the radiolucent area indicated a lung cyst, surgery was advised. Accordingly, an exploratory thoracotomy was performed and an emphysematous right upper lobe was found. There were blebs on the surface, and the lobe could not be compressed. The middle and lower lobes were atelectatic. No abnormalities could be found at the root of the lung to account for the obstruction of the bronchus. The lower segment of the upper lobe did not seem to be emphysematous. Right upper lobectomy was performed. The postoperative course was uneventful, the patient being discharged on the fourteenth postoperative day. His health has remained good.

Fig. 4 (Case 4).—C. F., aged 2 months. The upper two-thirds of the right lung were radiolucent while the lower third was almost completely opaque. The heart and mediastinum were shifted to the left. An emphysema of the right upper lobe was found at time of operation, but no lesion of the bronchus could be demonstrated.

Pathology: The upper two-thirds of the lobe were emphysematous; the lower third was atelectatic. In the emphysematous area, the bronchi were extremely dilated. In the atelectatic area, the bronchi were close together and collapsed. No lung cyst was found.

CASE 5.—M. J., a 7-week-old white male infant, was admitted to the hospital because of cyanosis brought on by crying and choking spells lasting only a few minutes. Beginning one week before admission, four such episodes occurred within one week. He was born of a normal pregnancy and delivery. No cyanosis was observed at birth. He had been developing normally with a good weight gain. Examination revealed respirations of 68 per minute with substernal retractions. The temperature was not elevated. Percussion and auscultation were nonrevealing. When placed in oxygen, the infant became comfortable.

Fig. 5 (Case 5).—M. J., aged 7 weeks, was seen to have severe emphysema of the entire left lung field with depression of the left diaphragm. The heart and mediastinum were shifted markedly to the right. It was thought that a portion of the left lung had herniated into the right side, and that there was atelectasis of the left lower lobe and possible compression atelectasis of the right upper lobe. A left upper lobe emphysema was found at time of operation, though a lesion of the bronchus was not demonstrated.

Roentgenograms: The heart and mediastinum were shifted markedly to the right, and there was considerable emphysema of the entire left lung field with depression of the left diaphragm. It was thought that a portion of the left lung had herniated into the right side, and that there was an atelectasis of the left lower lobe and possible compression atelectasis of the right upper lobe. (Fig. 5.) On the lateral view a large retrosternal space filled with air was noted and the mediastinal structures were probably pushed posteriorly.

Bronchoscopy: The trachea was deviated somewhat to the right. The right main and upper lobe bronchi were distorted and somewhat kinked, but not appreciably obstructed. The left main bronchus was obstructed by compression. The 3½ mm. bronchoscope was passed into this bronchus with considerable difficulty.

Course: A left exploratory thoracotomy was performed. The lingula and left lower lobe were found to be collapsed when the chest was first opened, while the superior portion of the upper lobe was greatly emphysematous. The left lower lobe could be expanded by pressure on the anesthetist's bag. Left upper lobectomy was performed, and the patient had an uneventful postoperative course.

Pathology: The superior portion of the lobe was emphysematous; the inferior portion completely collapsed. A secondary bronchus to the inferior portion of the lobe was obstructed by an inflammatory process. Other bronchi were not remarkable and there was no deficiency of the cartilagenous rings.

CASE 6.—Mention should also be made of case M. D., previously reported from this hospital by Lewis and Potts[8] "Obstructive Emphysema With a Defect of the Anterior Mediastinum." In this case an emphysematous right middle lobe was the cause of the symptoms. The lobe had herniated through the defect in the anterior mediastinum. No definite abnormality of the right middle lobe bronchus could be found. It is thought that the mediastinal defect may have contributed to the development of the emphysema.

The clinical course of these six patients may be briefly summarized. An infant or young child, previously well, is noted to suffer dyspnea or cyanosis or both, unrelated to a febrile pulmonary inflammatory process. Symp-

toms progress, and respond poorly to conservative therapy. The physical examination reveals hyperresonance and diminished breath sounds of one hemithorax or of a lobar area, with displacement of the heart and mediastinum away from the hyperresonant side. The radiographic findings are of a large area of localized radiolucency with shift of the heart and mediastinum away from the radiolucent side. The diaphragm of the radiolucent side is likely to be depressed. The area of radiolucency may be noted to be in the distribution of a single lobe, but frequently the lobe is so overdistended, it is difficult to recognize it as such. Partial atelectasis of other lung tissue on the same side or the other side may be present. The radiolucent area can be diagnosed as emphysema rather than pneumothorax, or single or multiple cysts, because lung markings are present throughout the entire area. Bronchoscopy and bronchography are of value mainly in excluding intraluminal causes of emphysema, the most important and most frequent of which is foreign body, either radiopaque or nonradiopaque. Exploratory thoracotomy reveals a greatly overdistended, emphysematous lobe which does not collapse upon opening of the chest. The dyspnea is relieved by removal of the compression on the normal lobes by the emphysematous lobe. The uninvolved lung tissue can be expanded by the anesthetist. The child makes a quick recovery following lobectomy, and returns to a normal life without disability. There have been no instances of recurrence of symptoms, and no other lobe has developed this syndrome after removal of the first affected one.

DISCUSSION

We are unable to explain the frequency with which we have recently observed this type of case, and the rarity of previously reported similar cases. A careful search of the world literature disclosed only the cases of Nelson,[9] Overstreet,[10] Biering,[11] Cassinelli,[12] Ferguson and Neuhauser,[13] Gross and Lewis,[14] Leahy and Butsch,[15] and the previously mentioned case of Lewis and Potts.[8] While this paper was in preparation, it came to our attention that two recent reports have been published on this same syndrome. "Congenital Lobar Emphysema" by R. Robertson and E. S. James[16] tells of five cases, three of the right upper lobe, one of the left upper lobe, and one of the right middle lobe. In two of the cases, valvelike folds of mucosa in the lobar bronchus were found, in one case a large vein appeared to constrict the appropriate bronchus, and in the other two cases no lesion was demonstrated. R. R. Shaw[17] in a paper on "Localized Hypertrophic Emphysema" reported one case of right middle lobe emphysema, and one case of emphysema of the subapical segment of the left upper lobe. He noted that the bronchus to the lobe or segment was abnormally flaccid.

Except for these cases reported, it seems that lobar emphysema of this type has either gone unrecognized or has been confused with other lesions. Lobar emphysema of a clinical type different than these occurring in children and infants has been recognized frequently as mentioned before.[18, 19] Congenital cystic lung disease, pneumothorax, and multiple bullae secondary to pulmonary inflammation could be confused with unilobar emphysema

clinically and roentgenographically. Now that the clinical picture and radiological findings are found to be distinct, this difficulty should no longer exist. It is difficult for us to conceive that emphysema of this severe degree with such pronounced tissue changes may spontaneously regress once the obstructive agent is removed, as would be the situation if a plug of mucus were removed by bronchoscopy. Yet this possibility must be considered as a cause of nonrecognition of this condition for advanced emphysema of a lobe or a lung subsides following the removal of a foreign body in the bronchus, and huge bullae have been observed to disappear when observed by serial roentgenograms in the postpneumonic period. The extent to which overdistention of the lung may be carried without permanent irreversible damage is not known, nor can it be gauged at time of operation.

The diagnosis, once one is aware of the possibility of occurrence, is not difficult. The first of our patients was operated on with the diagnosis of a giant lung cyst. Thereafter, the correct diagnosis was made preoperatively after endobronchial lesions had been excluded by bronchoscopy.

The etiology of these cases of lobar emphysema deserves further investigation. Malformation or rather deficiency of the cartilagenous rings of the bronchus was demonstrated to be the cause in two of our cases. In two other cases, a persistent ductus arteriosus was thought to be a causative factor. In each of these cases, the ductus overlay the main left bronchus, and, in each instance, the ductus was attached low on the left pulmonary artery. One of these ductus cases had an associated bronchial abnormality, but in the other case, no other cause save the unusual ductus was present. The occurrence of a left upper lobe emphysema when the left main stem bronchus was compressed leads one to suspect an additional factor concerned with the upper lobe alone. It is not unreasonable to have only upper lobe emphysema with compression of the main stem bronchus, if it is realized that the expiratory forces acting on the lower lobes are much greater than those acting on the upper lobes. The upward rising diaphragm and the more forceful movements of the lowermost ribs would more likely drive the air out of the lower lobe past a partial bronchial obstruction, whereas the upper lobe is acted upon more passively, more easily developing an obstructive emphysema. This point is supported by the fact that all of our cases, as well as the other reported cases, were of the upper or middle lobes, and none was of the lower lobes. In three of our cases, no bronchial lesions could be demonstrated, nor was any intrathoracic lesion noted at time of operation. An additional observation which further complicates the question of etiology is the atelectatic condition of the lingula with the upper lobe emphysema in Cases 3 and 5, and the collapsed condition of the lower third with emphysema of the upper two-thirds of the right upper lobe in Case 4. A second lesion in a smaller bronchus would account for this, and in Case 5, such a lesion, an inflammatory occlusion of the lingular bronchus, was found.

For lobar emphysema caused by a bronchial abnormality or an intrathoracic vascular lesion, lobectomy has been the only effective treatment. This

has been our experience and it is confirmed by the published reports. (We are not prepared to say how often a symptomless lobar emphysema occurs, but it does not seem to be often.) If the patient does not respond to bronchoscopy and conservative therapy, operation is indicated. An attempt to allow return to normal by restorative processes ordinarily possessed by the body has not been successful. Two of our patients were operated on as emergencies, and it is felt that death would have occurred if operation had been much delayed. Aspiration by needle or removal of the air by thoracotomy tube and water-seal drainage bottle may give some temporary relief but is not to be depended upon for permanent benefit. If a correctible vascular anomaly appears to be the only intrathoracic lesion at time of thoracotomy, lobectomy may be too radical a treatment. We were tempted to divide only the persistent patent ductus in Case 4, and not perform a lobectomy of the left upper lobe, but it was feared that the severity of the pathological process would never allow a return to a normal, functional state without residual emphysema.

SUMMARY

Lobar emphysema secondary to bronchial cartilage abnormalities, intrathoracic vascular abnormalities, and unknown causes is reported in five infants and children. The incidence, diagnosis, etiology, and treatment are considered.

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NIPPLE PAIN AND NIPPLE DAMAGE

Problems in the Management of Breast Feeding

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NIPPLE pain and nipple damage are pediatric problems because they are frequent causes of breast-feeding failure. The pain produced by an infant sucking on a traumatized nipple can be as severe as any pain suffered in the dentist's chair. A recent study in Philadelphia[1] revealed that over 80 per cent of breast-feeding mothers experienced nipple pain in the puerperium.

Nipple pain and nipple damage are sometimes related to severe pathological conditions. Leary[2] found that breast infections occurred much more frequently in women who had nipple fissures than in women who did not. Avoidance of nipple pain through the limitation of sucking leads to stasis in the breast[3] which in turn predisposes to mastitis. Klahn[4] found that mastitis occurred twice as frequently in incompletely emptied breasts.

Nipple pain has psychosomatic effects. The pain or the attempt to forestall the pain may cause sucking stimulation to be limited, thus curtailing the secretion of milk.[5] The pain may also inhibit the let-down reflex so that the milk already in the breast does not flow out to the baby.[6] When there is little milk flow, the negative pressure exerted by the baby on the nipple becomes very great and may lead to more nipple damage.[7]

Nipple pain may also have psychological repercussions. It prevents the mother from getting pleasure from the suckling act. It may make her dread feeding times or make her stop nursing altogether. The mother-child relationship gets a less favorable start because the first contact with the infant involves pain.

It seems unreasonable to suppose that nipple trauma is the necessary outcome of the baby's sucking. Lee[8] states that in pigs and dogs nipple trouble is very rare, although their nipples are similar to women's nipples. Mead[9] writes that: "In primitive society one finds . . . none of this type of irritated nipple which is so common among our mothers."

The problem, then, is: "What customs, practices or habits of thought do we have that are causing our mothers' nipples to be abnormally sensitive or weak?" The purpose of this study was to begin to find the answer to this question. Therefore, nipple pain and nipple damage were studied in relation to certain physical and mental factors and particularly in relation to nipple care.

METHODS

Two hundred eighty-seven mothers in the rooming-in maternity wards of the Jefferson Hospital in Philadelphia were included in this study. The mothers were divided into experimental groups. Those delivering their babies during a certain period were instructed to wash their nipples with soap solution* and water before each feeding. A second group was given 70 per cent alcohol and water

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*The soap solution was composed of 3 per cent medicinal soft soap U.S.P., 1 per cent Ultra Wet K (a synthetic detergent), 1 per cent Versene (a chelating agent).

for cleansing before feeding. The third group served as a control group and was given just water. The fourth, fifth, and sixth groups were given A and D ointment,* A and D concentrate,† and lanolin, respectively, with instructions to apply the compound after each feeding. These groups were also instructed to wash their nipples with water before feedings.

All the mothers were seen by the same investigator. Each time each mother was interviewed she was asked how her nipples felt when the baby nursed on them. An effort was made to avoid questions that might suggest pain to the mother. The mothers were also asked about their use of the recommended experimental nipple preparation, how many times they fed their babies in the last twenty-four hours, and other similar questions related to the state of their nipples. Records were kept of the answer to each question. In addition, during each interview the nipples were examined and details of their appearance recorded. The last 174 mothers were admitted to the hospital at a time when data were being collected for a study on women's attitudes toward motherhood and their unique biological functions. Thus considerable data about these women are available in addition to the data collected for the nipple pain study. The methods for collecting these data are fully described elsewhere.[10]

This study includes the first through the fifth post-partum days. It was not possible to see every mother every day. Some babies were not yet nursing at the time of the first-day interview, and on the fourth and fifth days mothers and babies were in the process of going home. In addition, some observations had to be excluded because several mothers gave no definite assurance that they were using the nipple preparation. Sometimes mothers started using the preparation and then ceased to use it after their nipples became tender. All data collected after mothers had stated they had ceased to use the preparation for more than one day were discarded. The odor of the A and D concentrate made it particularly unpopular with the mothers. To assure the use of A and D concentrate one or two drops were put on each nipple during the interview. Since the effect of water alone was assumed to be negligible, no inquiry was made about the use of water, and no cases were excluded on the grounds of not using it.

Each case was given a nipple pain and nipple damage rating for each day of observation. The rating of *negligible pain* was given when the mother reported no soreness or slight soreness which disappeared shortly after the baby began to suck. The rating of *definite pain* was given when the mother reported soreness, tenderness, stinging or biting that disappeared after the baby had sucked for a little while *or* slight soreness that stayed throughout the nursing. The rating of *extreme pain* was given when a mother reported soreness that kept on throughout the entire nursing period or pain continuing between feedings. The rating of *normal nipple* was given when the nipple was described as nor-

*The A and D ointment (a product of White Laboratories) derived its vitamin content from fish liver oils and its vehicle was essentially a mixture of lanolin and petroleum.

†The A and D concentrate (a product of White Laboratories) was a concentrate of pure cod-liver oil in which the vitamin A potency was adjusted and standardized with fish liver oils and D potency supplied entirely by cod-liver oil concentrate.

mal, dry,* or only slightly traumatized. The rating of *damaged nipple* was given to nipples which were fissured, eroded, definitely irritated, raw, or had formed crusts. As a check on the reliability of the ratings, a surgeon was asked to pick five case records at random from each of six experimental nipple preparation groups. His ratings agreed with those of the experimenter in 90 per cent of the nipple pain ratings and in 93 per cent of the damage ratings.

Usable data about pain were available in 163 mothers on the first day, 229 on the second day, 232 on the third day, 179 on the fourth day, and 88 on the fifth day. Data about both nipple pain and nipple damage were available for the same mother on the same day except in ten instances when either the pain or the damage rating was lacking for one day. On all days considerably more mothers were in the control, soap, and alcohol group than in the groups given hydrous lanolin, A and D ointment, and A and D concentrate.

All the usable data were used in compiling Tables I, II, and III which concern the experimental use of various types of nipple care. Table IV is based on the ninety-one mothers who were in either the control or the hydrous lanolin group and for whom third-day ratings of pain and damage were available. The third-day records were used since this day usually showed the highest incidence of pain and damage. The hydrous lanolin group was used with the control group because the incidence of the pain and damage in these two groups is very similar. In each item tabulated in Table IV some cases were omitted due to lack of information but the number of these omissions is not appreciable except in the case of length of labor when the total number of cases was reduced to fifty-six. Data about nipple care are added at the end of Table IV for comparative purposes and are based on the same cases covered in Tables I, II, and III. The second-day data were used in the nipple care groups since this day showed the most marked differences.

After the data were tabulated, percentages and chi-squares were calculated. Yates's correction for continuity was applied to all chi-squares, thus yielding conservative estimates of probabilities. Phi coefficients were calculated for the data presented in Table IV since an estimate of the degree of relationship was considered desirable. The phi coefficient is a product moment correlation coefficient designed to fit the two-by-two table.

RESULTS

The results of this study are summarized in Tables I, II, III, and IV.

DISCUSSION OF RESULTS

The results of this study will be discussed under three main subdivisions: (A) Factors influencing the health of the nipple skin; (B) immediate preventive measures; and (C) treatment. First, however, the tentative nature of this research study should be emphasized. The application of the various compounds was left to the mothers and the degree to which they used them varied greatly. The rooming-in environment made it difficult to control some factors easily con-

*As ointments tended to make the skin appear oily, dryness could not be used as a measure of the success of the ointment. It should not be assumed that the dry nipple is actually a completely normal nipple. In the control group on the third day 56 per cent of the mothers who had dry nipples reported pain as compared with 41 per cent of those who had completely normal-looking nipples.

TABLE I. DAILY INCIDENCE OF PAIN IN MOTHERS USING VARIOUS TYPES OF NIPPLE CARE[1]

	% REPORTING DEFINITE OR EXTREME PAIN ON FIRST DAY	% REPORTING DEFINITE OR EXTREME PAIN ON SECOND DAY	% REPORTING DEFINITE OR EXTREME PAIN ON THIRD DAY	% REPORTING DEFINITE OR EXTREME PAIN ON FOURTH DAY	% REPORTING DEFINITE OR EXTREME PAIN ON FIFTH DAY
Controls	32	51	65	50	(27)
Alcohol	28	70‡	81†	75‡	65†
Soap	(42)	62	78	67	(56)*
Hydrous lanolin	(35)	58	69	50	(47)
A and D ointment	(39)	(61)	65	(50)	(33)
A and D concentrate	(43)	50	50	(31)*	(33)

[1]Percentages based on less than twenty cases are in parentheses.

*The probability that the difference between this and the control group is due to chance is between .20 and .10.

†The probability that the difference between this and the control group is due to chance is between .10 and .05.

‡The probability that the difference between this and the control group is due to chance is between .05 and .02.

TABLE II. DAILY INCIDENCE OF VISIBLE DAMAGE IN MOTHERS USING VARIOUS TYPES OF NIPPLE CARE[1]

	% SHOWING DAMAGE ON FIRST DAY	% SHOWING DAMAGE ON SECOND DAY	% SHOWING DAMAGE ON THIRD DAY	% SHOWING DAMAGE ON FOURTH DAY	% SHOWING DAMAGE ON FIFTH DAY
Controls	15	29	44	32	(25)
Alcohol	36‡	46†	50	49	60
Soap	(16)	47*	58	63§	50
Hydrous lanolin	(6)	24	31	27	(31)
A and D ointment	(31)	(28)	35	(18)	(33)
A and D concentrate	(43)†	55†	50	(50)	(50)

[1]Percentages based on less than twenty cases are in parentheses.

*The probability that the difference between this and the control group is due to chance is between .20 and .10.

†The probability that the difference between this and the control group is due to chance is between .10 and .05.

‡The probability that the difference between this and the control group is due to chance is between .05 and .02.

§The probabili y that the difference between this and the control group is due to chance is between .02 and .01.

TABLE III. THE TYPE OF PAIN EXPERIENCED IN VARIOUS NIPPLE CARE GROUPS[1]

	% HAVING EXTREME PAIN	% HAVING DEFINITE PAIN
Controls	32	68
Alcohol	29	71
Soap*	43	57
Lanolin	27	73
A and D ointment	29	71
A and D concentrate†	60	40

[1]This table is based on the total number of reports of pain made on all five days. The number of reports involved is 107 for controls, 148 for alcohol group, 94 for soap group, 75 for lanolin group, 41 for A and D ointment group, and 35 for A and D concentrate group.

*The probability that the difference between this and the control group is due to chance is between .10 and .20.

†The probability that the difference between this and the control group is due to chance is less than .01.

(Cont'd from opposite page.)

[9]This phi coefficient is based on the incidence of pain or damage in mothers who used A and D ointment vs. mothers who used water (controls).

[10]This phi coefficient is based on the incidence of pain or damage in mothers who used A and D concentrate vs. mothers who used water (controls).

[11]Mothers often reported that they kept the baby in bed with them all night and that the baby sucked intermittently during this time. All such mothers were put in the 9 or over feedings per day group.

[12]The most frequently used ointments were petroleum, Mother's Friend, and olive oil. No definite differences in incidence of pain or damage could be noted between the small groups of users of each of these items.

TABLE IV. THE RELATIONSHIP OF NIPPLE PAIN AND DAMAGE TO VARIOUS PHYSICAL AND MENTAL FACTORS

	% HAVING PAIN	PHI COEFFICIENT	% HAVING VISIBLE DAMAGE	PHI COEFFICIENT
Mental Factors				
Attitude toward pregnancy				
Did not mind pregnancy	62		41	
Complains about pregnancy	69	.07	33	-.08
Attitude toward birth				
Thought birth was easy	57		48	
Thought birth was hard	69	.12	31	-.16
Attitude toward lactation				
Wants to breast feed	69		46	
Doubtful about breast feeding	63	-.07	28	-.19*
Attitude toward care of baby				
Likes rooming-in	62		34	
Complains about rooming-in	78	.14	44	.09
General Physical Factors				
Health during pregnancy				
Healthy (including Rh-negative mothers)	67		35	
Complications	61	-.07	39	.05
Parturition				
Normal	67		39	
Complications (including episiotomies)	65	-.02	35	-.03
Length of labor				
Less than 15 hours	67		35	
More than 15 hours	69	.02	46	.10
Use of Nipple				
Parity				
1 child	62		44	
2 or 3 children	77	.15[1]	41	-.03[1]
4 or more children	50	-.18[2]*	25	-.17[2]
Previous nursing experience				
Previous baby breast fed	68		33	
No previous baby breast fed	70	.01	52	.17*
Number of feedings in last 24 hours				
5 and under	69		38	
6, 7, and 8	64	-.05[3]	39	.01[3]
9 and over[10]	68	.05[4]	39	.01[4]
Number of feedings on previous day				
5 and under	50		27	
6, 7, and 8	62	.12[3]	46	.20[3]
9 and over[10]	80	.21[4]	40	-.07[4]
Nipple Care				
Prenatal care				
No ointments applied	67		43	
Ointments applied[11]	70	.03	37	-.06
Postnatal care				
Water (controls)	51		29	
Alcohol	70	.20‡[5]	46	.17†[5]
Soap	62	.11[6]	47	.18*[6]
Hydrous lanolin	58	.06[7]	24	-.05[7]
A and D ointment	61	.09[8]	28	-.04[8]
A and D concentrate	50	-.01[9]	55	.23†[9]

*The probability that this relationship occurred by chance is .20-.10.

†The probability that this relationship occurred by chance is .10-.05.

‡The probability that this relationship occurred by chance is .05-.02.

[1]This phi coefficient is based on the incidence of pain or damage in primiparas vs. mothers who have two or three children.

[2]This phi coefficient is based on the incidence of pain or damage in mothers who have two or three children vs. those who have four or more.

[3]This phi coefficient is based on the incidence of pain or damage in mothers who fed their babies 5 and under times vs. those who fed their babies 6, 7, or 8 times.

[4]This phi coefficient is based on the incidence of pain or damage in mothers who fed their babies 6, 7, or 8 times vs. those who fed their babies 9 or more times.

[5]This phi coefficient is based on the incidence of pain or damage in mothers who used alcohol vs. mothers who used water (the controls).

[6]This phi coefficient is based on the incidence of pain or damage in mothers who used soap vs. mothers who used water (controls).

[7]This phi coefficient is based on the incidence of pain or damage in mothers who used hydrous lanolin vs. mothers who used water (the controls).

(Footnotes continued on opposite page.)

trolled in a conventional hospital. On the other hand, rooming-in had the advantage of testing nipples under normal, rather than artificially restricted, lactation conditions.

A. Factors Influencing Health of Nipple Skin

Tables I and II show that the use of soap solution was related to a high incidence of nipple pain and nipple damage. Mothers using soap on their nipples experienced both more pain and more damage on all five days of the study than did the control group. The difference in the incidence of visible damage on the fourth day was statistically significant at the .02 level. In addition to causing more pain, soap caused more extreme pain as shown in Table III. Forty-three per cent of the pain experienced in the soap group was extreme in nature as compared with 32 per cent in the control group.

It is important to keep in mind that the soap solution was rendered more potent by the addition of a synthetic detergent which increased the defatting effect of soap, and a chelating agent which increased the alkalinizing effect of soap. However, there is evidence that pure soap alone may weaken the skin in four days.

1. Soap (through mechanical action) removes the dead horny cells and material derived from their alteration and disintegration which form part of the protective covering of the skin.[11] Alkaline watery solutions such as soap also swell the outer epidermal layer which normally contains only 7 to 20 per cent water.[12] The swelling is followed by drying, loosening, and scaling of cells.[11]

This removal of the outer epidermal layer is cumulative[11] as the applications of soap are repeated.

2. Soap removes the secretions of the sebaceous glands.[11] The sebum is also an important contributor to the protective covering of the skin,[11] and helps to keep the skin pliable.[14]

3. Soap alkalinizes the skin. All soap, no matter how mild, hydrolyzes in water to form an alkaline solution.[11] The normal skin has a definite capacity for neutralizing alkali, but experiments show that it takes the skin some time to recover its normal acidity after it has been alkalinized.[13] When skin is alkalinized the bacterial flora increase.[13]

4. Soap removes the secretions of the sweat glands which may help to keep the skin pliable and normally acid.[11, 14]

Probably the reason why the harmful effect of soap on the skin seldom is noticed is that the skin of civilized people usually is protected from hard usage. The nipple skin during lactation is not so protected, but is subject to the same stress and strain that the skin of all mammals gets at such times.

It is usual for women to use particularly generous quantities of soap on their nipples during pregnancy and lactation. This effectively counteracts the effort of the body to prepare the nipple for the abrasive and stretching action of sucking. During pregnancy the secretion of sebum becomes copious and the sweat glands hypertrophy.[14] Daily soaping removes both sebum and sweat[11] and destroys their protective action.

One step in the prevention of nipple pain and nipple damage would seem to be to instruct the pregnant and lactating woman to avoid the use of

soap on her nipples.* She might be told that the skin on her nipples may alter in appearance, but that this is not dirt but merely her body's way of preparing the nipple to withstand the force of the sucking infant.

Tables I and II show that the use of alcohol on the nipples was related to a higher incidence of nipple pain and nipple damage. Mothers using alcohol on their nipples reported more pain than the control group on the second, third, fourth, and fifth days, and showed more visible damage on all five days. These differences are statistically significant at the .05 level in the case of pain on the second and fourth days and in the case of damage on the first day. The results of this study are entirely in keeping with what is known about the pharmacological action of alcohol. Concentrated alcohol hardens tissues by abstracting their water and precipitating the protein.[15] This leaves the skin less pliable and more prone to fissure.

The effect on the nipple of other commonly used substances, such as benzalkonium chloride solution U.S.P. or boric acid, is untested and unknown. Since alcohol and soap are often regarded as harmless, yet appear to be harmful, it would seem wise to regard other antiseptic substances with suspicion.†

The idea that the human nipple should be treated as much as possible like a rubber nipple may arise from the fact that medical schools and nursing schools spend so much more time teaching the technique of artificial feeding than of successful breast feeding. I was able to find no direct evidence that it is advantageous to attempt to make the human nipple practically sterile. On the other hand, there is a well-recorded instance of an epidemic of diarrhea which occurred in conjunction with the putting of boric acid solution from a common container onto the mothers' nipples.[16]

The human body, when not interfered with, has mechanisms which probably greatly reduce the number of bacteria on the nipple. The largest sweat glands in the body are found in the nipple.[14] Sweat with sebum has bactericidal properties.[14] In addition this newly secreted human milk has an antibacterial action.[17] The lyzozym content of human milk is reported to be 100 times as great as that of cow's milk.[18]

The second step in the prevention of nipple pain and nipple damage would seem to be eliminating all attempts to make the human nipple sterile. Such attempts at antisepsis are unnecessary since the body has its own mechanisms for controlling bacterial flora, and may weaken the skin at a time when its strength is most needed.

The effect of some other factors that might be related to nipple pain and nipple damage are shown in Table IV. The only relationships of the order of those found in the use of soap and alcohol (i.e., phi coefficients of around .20) were to be seen in connection with attitudes toward breast feeding and in the various indices of nipple use. None of these relationships were statistically significant at the .05 level, but they show some possible trends.

Mothers who wanted to breast feed experienced 18 per cent more nipple damage than those who were doubtful about breast feeding. This is in line

*Neutral synthetic detergents would avoid the alkalizing effect of soap but could be expected to remove the sebum, sweat, and some portions of the outer epidermal layer.

†Since benzalkonium chloride has a basically detergent action (lowers surface tension), it could be expected to produce a condition similar to soap.

with the previous work of Newton and Newton[19] who found that more nipple fissures occurred in the mothers who wanted to breast feed than in those who were doubtful or negative about breast feeding. The most reasonable explanation for this is that mothers who wanted to breast feed allowed their babies to suck more and thus subjected their nipples to more strain.

Although the number of feedings on the same day had little relation to pain and damage, the number of feedings on the previous day was related to pain and damage. This, like the correlation in the case of breast feeding attitudes, suggests that the amount of sucking is an important factor in causing nipple complications. This finding is in line with the work of Gunther[7] who found that significantly more sore nipples occurred in mothers of heavy babies who could presumably suck more vigorously.

Just how sucking causes nipple damage is an interesting question. Gunther,[7] using an ingenious device, demonstrated that the sucking infant builds up high negative pressure on the nipple. She hypothesizes that the erosive type of nipple lesion is actually a petechial lesion of extravasated blood. I, like Gunther, observed two markedly different types of nipple damage, but feel that erosive rather than petechial best describes the type of lesion in question since all the skin rather than just its blood supply appears to be involved.

Health during pregnancy, normality of parturition, length of labor, or the use of ointments on the nipples before birth seem to have little relation to nipple problems. Mothers who felt rooming-in and birth were difficult quite naturally also showed a slight tendency to complain more about nipple pain.

There are, of course, many other factors that might be involved in the health of the nipple skin which were not included in this study. The nipple is seldom exposed in our culture. Thus it is protected from abrasion, changes of temperature, and sunlight. All of these factors might well leave it in a weaker condition to meet its sudden hard use. The abnormally dry air so typical of overheated hospitals and homes during the winter months is believed to have a definite drying effect on the skin[12] and thus might weaken its resistance to sucking.

The possibility of dietary origin of nipple weakness should be kept in mind. Subclinical vitamin deficiencies occur very frequently in pregnant women of our culture[20] and it is well known that diet influences the health of the skin. Lack of vitamin A interferes with the growth and maintenance of the epithelial cells and causes atrophy of the sweat and sebaceous glands.[14] The health of the skin is also impaired by the lack of B complex and by lack of essential amino acids.[14] Gunther,[7] who believed that the cause of erosive nipple damage was chiefly vascular, tried administering large doses of vitamin C. She found no significant difference between the experimental and control groups.

Hormonal factors may also be involved. Gunther[7] and Ham[21] suggest that since estrogen may be lacking in the puerperal woman, and that since the epidermis of the nipple is sensitive to estrogens, the nipple suffers from lack of estrogenic stimulation. This predisposes it to injury. This theory is hard to reconcile with the

fact that sore nipples in most mammals are very rare, yet it is important because of its suggestion that hormonal factors should not be ignored.

B. Immediate Preventive Measures

Although the prevention of nipple complications through building up the health of the nipple skin is by far the most desirable method, this is impossible to do in many instances. The problem then arises as to what can be done to forestall trouble in a more direct way.

The favorite method at the present time is seriously to restrict sucking stimulation. No practice could be more harmful to lactation as a whole. It has been shown repeatedly that it is sucking which stimulates the secretion of milk.[5] The normal mammalian pattern is for lactation to be initiated immediately after birth and this is followed by frequent feeding during the immediate post-partum period. This is also the pattern established in human mothers and infants when hospital routines do not prevent this. At Jefferson Hospital 49 per cent of the mothers of the control and lanolin groups reported on the third day that they were nursing their babies nine or more times a day or were sleeping with them at their breast at night. At the Yale rooming-in project babies receiving only breast milk nursed on an average of 135 minutes on their second day and over 140 minutes a day on the third, fourth, fifth, sixth, and seventh days.[22]

Nor is the limitation of the number of feedings as effective a deterrent to nipple pain and nipple damage as might be believed. To a certain extent it merely postpones the difficulty. Thus in the rooming-in series the peak of the pain occurred on the third day and nipples were getting better by the fourth day. In a hospital which allowed six long feedings a day, the nipples continued to get worse until the fourth day.[1]

Another way in which sucking is restricted is by attempting to limit the number of minutes the baby is at the breast during the first few days. It is almost universal nursing practice to warn the mother not to allow the baby to suck more than three to five minutes at the beginning of lactation.* This procedure probably protects the nipple very little. If pain is any indication of when the most trauma is occurring, the first minute of sucking is overwhelmingly the most damaging. Sixty-two per cent of the mothers in the control group who had pain on the third day reported that they experienced pain only during the first few sucks the infant took.

The limitation of sucking is harmful in many ways. It leads to incomplete emptying of the breast and thus causes engorgement[3] and predisposes to mastitis[4] and breast abscesses.[23] Another objection to the limitation of time at the breast is that there seem to be individual differences in the time taken for nipple erection and let-down reflex to occur. Thus the shy young mother unconditioned to letting down her milk will just be getting nursing underway when the time is up. Furthermore, clock watching may make her feel tense, spoil her enjoyment of breast feeding, and inhibit her let-down to the baby even more.

*Whether or not the mother accepts the advice probably depends on her attitude toward breast feeding, toward her baby, and toward authority. Most of the mothers in the rooming-in wards of Jefferson Hospital did not let the clock deny their babies more time at the breast if the babies seemed to want it.

There is, however, evidence that sleepy, unproductive sucking at the breast may be harmful since it builds up high unrelieved negative pressures.[7] There would seem to be little harm and perhaps some benefit from instructing the mother to take the baby off the breast after it seems to have had a meal and relapses into sleep. Showing the mother how to break the suction by inserting her finger along the nipple before she removes the baby may save her many an acutely painful moment, and protect her nipple from further damage.

Better methods than the limiting of sucking must be found for protecting the nipple. With this in mind, ointments that might be helpful were studied. Petrolatum and ointments with petroleum bases are commonly used on the nipples at the present time. Petrolatum does form a protective coating which has been experimentally demonstrated to be excellent.[24] However, petroleum products inhibit the insensible evaporation of sweat from the skin thus causing the horny layer to swell with unevaporated moisture and become macerated.[12] Under such conditions microorganisms may flourish.[12] In addition petroleum products have a defatting action on the skin.[25] Recent work on animals shows that healing is definitely impeded when petrolatum is put on injured animal skin.[26] Olive oil is also frequently recommended. Here again recent experimentation shows that it causes acanthosis and parakeratosis on hairy animal skin to an even greater degree than does mineral oil.[27]

Lanolin was chosen as the ointment to test because it forms a protective coat that is as highly resistant to penetration as is petrolatum, and more resistant than other types of ointments.[24] Yet hydrous lanolin does not seem to have irritating qualities.[27] Lanolin is miscible with water and thus allows normal evaporation from the skin. Tables I and II show that the hydrous lanolin group was in no way significantly different or even consistently better or worse than the control group. Table III indicates this group had had slightly less extreme pain than the control group, but this difference might easily have occurred by chance.

There is some clinical belief that vitamins A and D locally applied speed healing,[28] and there is evidence that cod-liver oil has superior skin-penetrating powers.[29] Therefore it was decided to test A and D concentrate which consisted of concentrated cod-liver oil with other fish oils.

A and D concentrate appeared to be highly irritating to the nipples of some mothers. Whereas the percentage experiencing pain was sometimes more, sometimes less, than the control group, the severity of the pain was decidedly different. Thus 60 per cent of the pain experienced by the A and D concentrate group as compared with 32 per cent in the control group was extreme in nature. This difference is significant at the .01 level. On all five days a higher proportion of the A and D concentrate group had damaged nipples as compared with the control group. This difference was particularly marked during the first two days. This suggests either that A and D vitamins in highly concentrated quantities have an irritating effect on the skin or that the oil itself was irritating.

A and D ointment was also tested. Tables I, II, and III show that the

group of mothers using A and D ointment was not consistently or significantly different from the control group. Brougher[30] noted, as I did, that the application of A and D ointment on sore nipples often gave the mother some sort of psychological relief or satisfaction. He found five out of 200 mothers who used A and D ointment prophylactically developed fissures as compared with fifteen out of 200 mothers who used other unspecified forms of nipple care.

C. Treatment

The last problem involved in nipple pain and nipple damage is how to treat them once they arise. First, further injury of the skin should be avoided. For instance, compound tincture of benzoin is routinely used on sore nipples in many hospitals. The results of this study indicate that alcohol, which is the base of compound tincture of benzoin, has a definitely deleterious effect on the nipple skin.

New evidence re-emphasizes the old idea that skin heals most quickly when left alone, dry and exposed.[31] In line with this reasoning rubberized nursing brassières and heavy breast binders should not be used in the early puerperium.

It seems unnecessary to harm the chances of lactation as a whole by removing the baby from the breast unless damage is extraordinarily severe. The control group, whose nipples were not traumatized by sundry applications, had nipples which seemed to heal rapidly without the removal of the baby from the breast.* Thus 65 per cent had pain on the third day which fell to 27 per cent on the fifth day. Forty-four per cent showed damage on the third day as compared with 25 per cent on the fifth day. Although lactation was not entirely stopped, the mothers tended to spare their sorest nipple and to use the other one more. Perhaps the recommendation that nursing should start on the less sore nipple and proceed to the sore nipple in five minutes' time might be helpful to some mothers since once the let-down reflex makes the flow of milk from the nipple readily available, less negative pressure is present. Crusts that form on an eroded nipple should not be removed even though they look "dirty" to the fastidious. Once these crusts form securely they seem to protect the nipple and mitigate the extreme pain.

Medical literature is replete with suggested remedies for sore nipples. The belief in the effectiveness of various substances may have arisen from the fact that incidence of nipple pain may tend to decrease regardless of care the nipples receive, unless such care is unusually injurious. Table I shows that the incidence of pain in every nipple care group fell between the third and fourth day, and fell again between the fourth and fifth day in every group except in the A and D concentrate group.

There is nevertheless one piece of advice often given to mothers that this study indirectly substantiates. Previous nipple use is related to a lower incidence of nipple complications. Table IV shows that 33 per cent of mothers who had breast fed the previous baby had nipple damage as compared with 52 per cent of the primiparas and women who had not breast fed other babies. Parity may also be

*Nipple shields were available but few mothers in the control group made use of them. Nipple shields were used more widely by the mothers in the alcohol and soap groups.

considered as a rough index of nipple use. Those with four or more children both reported less pain and showed less damage.* This suggests that it might be useful to advise mothers to try to stimulate use before parturition. This could be simply done by holding the nipple in a rough towel and pulling outward several times.†

A mother has a right to some relief from nipple pain which is severe enough to make her dread giving the baby her breast. The prescription of a mild analgesic to be taken shortly before the time of expected feeding can help make the pain bearable. Perhaps for some mothers the ideal analgesic is a mild alcoholic drink such as beer or wine since there is a little evidence that it also helps let-down,[6] and is more pleasant to take than pills.

Even pain without visible damage calls for attention. Gunther,[7] Brougher,[30] and I all noted pain without visible damage. The report of pain without visible damage is not necessarily of purely psychological origin. In the lanolin and control groups on the third day 28 per cent of the mothers who wanted to breast feed reported pain but showed no damage as compared with 38 per cent of the mothers who were doubtful about breast feeding—a difference of only 10 per cent. In contrast to this, 25 per cent of the mothers in the same groups who had pain but no damage on the second day developed visible damage by the third day. Extreme pain usually occurred in conjunction with visible damage, and only 2 per cent of the control group on the third day had visible damage without the admission of any pain. Neither pain nor damage should be ignored or considered "just natural." Prevention and alleviation are worthy of the attention of the physician as well as the nurse.

*Why there was a tendency for women with two or three children to report more pain than those with one is difficult to understand, except on the basis of chance.

†The psychological effect of prescribing this or other lactation rituals should be considered. Elaborate preparations for breast feeding make many mothers feel that lactation is a bother, rather than a natural easy process. However, lactation rituals may help some mothers by making them think lactation is important and bolstering their confidence in their ability to produce milk. The same psychological effect may be achieved more simply by having the puerperal care of mother and baby under the direction of a nurse who has successfully breast fed several children of her own.

SUMMARY

Nipple pain and nipple damage were studied in 287 mothers in the rooming-in maternity wards of the Jefferson Hospital. Significantly more nipple trauma was found in mothers using alcohol, soap solution, or A and D concentrate on their nipples, as compared with the control group. Mothers using A and D ointment and hydrous lanolin had an incidence of pain and damage similar to the control group, although slightly less severe pain was noted. Number of feedings on the previous day, parity of the mother, experience of breast feeding a previous baby, and attitude toward lactation also were related to the occurrence of nipple trauma in the group studied.

CONCLUSIONS

Nipple pain and nipple damage are important because they are related to undesirable psychological, psychosomatic, and physical conditions, and because they may particularly afflict mothers who want to breast feed. There is need for more research on the prevention and treatment of nipple pain and nipple damage. Until further research is available the following suggestions can be made:

1. Avoid the use of soap on the nipple during pregnancy and lactation, since soap may counteract the body's efforts to prepare the nipple skin for abrasion and stretching.

2. Avoid attempts to partially sterilize the nipple skin, since these measures are unnecessary and sometimes harmful.

3. Allow the baby to suck when he wants and as much as he wants, except for preventing sleepy sucking at the end of a satisfying meal. The limitation of sucking induces lactation failure and other severe complications.

4. Keep the nipple dry and exposed to free circulation of air since this promotes healing.

5. Keep the baby on the breast unless unusually severe damage is present. Rapid healing usually occurs in spite of sucking when the nipple is not traumatized by soap, alcohol, compound tincture of benzoin, petrolatum, or other harmful substances.

6. When pain is severe, prescribe a mild alcoholic beverage or other analgesic to be taken shortly before time of expected feeding.

7. When mother and physician feel they must do something active to the nipple, applications of lanolin or A and D ointment appear to do no harm and may be slightly beneficial.

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FURTHER STUDIES ON THE BLOOD OF CHILDREN WITH CYANOTIC HEART DISEASE WITH SPECIAL REFERENCE TO THE HEMOGLOBIN

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ALTHOUGH the physiologic effects of anoxia due to high altitude have been carefully studied, much less attention has been devoted to the effects of chronic anoxia resulting from disease processes. Bing and associates[1] and Morse and co-workers[2] have studied certain aspects of the adaption process in children with cyanotic heart disease. Wilson, Borden, and Ebert[3] have studied the adaption to anoxia in chronic pulmonary emphysema. In two previous communications,[4, 5] we have alluded to our interest in studying the adaptive mechanisms in children with cyanotic heart disease. It was anticipated but not substantiated by us that there might be a persistence of some *fetal mechanism* in such cyanotic children.

The purpose of this communication is to report further studies on the above-mentioned fetal mechanism including the hematopoietic system. Particular reference will be made to the alkali denaturation rate of the hemoglobin from such cyanotic children.

HEMATOLOGIC STUDIES

These studies have been reported in part elsewhere,[4, 5] but in view of the additional information obtained, it seemed of value to summarize all of our experience in this regard. Eighteen children with moderate to severe cyanotic heart disease were studied for the following: the hemoglobin, the red blood cell count, the hematocrit, the mean corpuscular diameter, and the carbonic anhydrase content of the red cells. Additional observations were made on a different group of individuals but with equally severe cyanotic heart disease; these included the red cell fragility, the reticulocyte count, the platelet count, and the bone marrow.

Determinations of the hemoglobin content of the blood were performed on a Junior Coleman Spectrophotometer which was standardized with blood of known hemoglobin content as determined by the oxygen capacity method. The red blood counts were done by one individual using calibrated pipettes. The hematocrit determinations were obtained by centrifuging blood with heparin as an anticoagulant in 4 c.c. hematocrit tubes at 3,000 r.p.m. for thirty minutes. The mean corpuscular diameter was obtained by using a Haden-Hausser erythrocytometer. The carbonic anhydrase content of the red blood cells was determined by the method of Lambie.[6] Cell fragility determinations were done according to a technique described by Suess and associates[7] and slightly modified by us.[5] The reticulocyte and platelet counts

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were done in the usual manner described by Todd and Sanford.[8] Bone marrow studies were made according to the method described by Sundberg.[9]

RESULTS OF HEMATOLOGIC STUDIES

The results of the hematologic studies on the peripheral blood can be seen in Table I. From this table, it can be seen that the age range was ¾ to 24 years with a mean of 12 years for the eighteen observations on the hemoglobin, the red blood cell count, the hematocrit, the mean corpuscular diameter, and the carbonic anhydrase. The twenty-seven who were tested for the red cell fragility had an age range of 1 to 14 years with a mean of 7 years. The sixteen who were checked for their platelet counts had an age range of 1 to 15 years with a mean of 5 years, and the seven who were checked for their reticulocyte counts had an age range of ⅓ to 15 years with a mean of 6 years.

The means were as follows: the hemoglobin, 18.3 grams per cent; the red blood cell count, 7.84 million per cubic millimeter; the hematocrit, 63 per cent; the mean corpuscular diameter, 6.6 μ; the reticulocyte count, 0.7 per cent; the platelet count, 117,000 per cubic millimeter; the carbonic anhydrase content 3.12 units; and the cell fragility began at 0.54 and was complete at 0.33 per cent saline.

TABLE I. OBSERVATIONS ON THE BLOOD OF CHILDREN WITH CYANOTIC HEART DISEASE

STUDY	NO. OBSER.	AGE RANGE (YR.)	MEAN AGE	RANGE OF VALUES	MEAN OF VALUES	NORMAL VALUE
Hemoglobin grams %	18	¾-24	12	13.3-24	18.3 gm.	13.0
R.B.C./million	18	¾-24	12	4.64-13.9	7.84 m.	4.78 m.
Hematocrit %	18	¾-24	12	32-80%	63%	41%
MCD size	18	¾-24	12	6.0-7.3	6.6	7.0
Retic. %	7	⅓-15	6	0.4-1.7%	0.7%	1.0%
Platelets per cu. mm.	16	1-15	5	60,000-200,000	117,000	250,000
Carbonic anhydrase	18	¾-24	12	2.11-4.50 units	3.12 units	1.85 units
Cell fragility	27	1-14	7	Start .45-.90 Complete .36-.27	.54 .33	.53 .33

TABLE II. BONE MARROW PATTERNS OF CHILDREN WITH CYANOTIC HEART DISEASE

NAME	S. C.	E. S.	R. S.	R. R.	C. S.	D. K.	L. M.	B. H.	D. C.	R. F.	MEAN
Age	3	11	10	4	8	9	13	1 mo.	2	11	7.2
Sex	M	F	M	M	F	F	M	F	M	M	–
% Plasma	32	12	18	14	36	19	34	35	59	21	28
% M-E layer	4	4	9	11	9	5	9	9	8	10	8
% R.B.C.	64	85	73	76	54	77	54	46	34	69	63
% Fat	0	tr.	1	0	2	tr.	3	tr.	tr.	1	tr.
% Normoblasts	25	39	22	40	28	38	20	31	25	25	29
% Neutrophils	48	40	56	39	43	36	49	32	57	52	45
% Eosinophils	2	3	2	4	9	3	3	5	2	2	4
% Lymphocytes	3	16	20	17	20	23	27	30	20	18	19
No. Megakaryocytes	88	192	184	113	486	112	620	374	23	108	230
Site	S	I	S	I	I	I	S	I	I	S	--

S = Sternum.
I = Ilium.
T = Tibia.

The results on the bone marrow aspirations on ten children with cyanotic heart disease can be seen in Table II. The age range was 3 to 11 years. The means were as follows: 28 per cent plasma; 8 per cent myeloid-erythroid layer; 63 per cent red blood cells; trace of fat; 29 per cent normoblasts; 45 per cent neutrophils; 4 per cent eosinophils; 19 per cent lymphocytes; 230 megakaryocytes per terminal—18 × 18 sq. mm.

HEMOGLOBIN DENATURATION STUDIES

The method of Singer and collaborators[10] was used to study the resistance of the hemoglobin to strong alkali. Briefly, an approximately 10 per cent hemoglobin solution was prepared from fresh oxalated blood, employing distilled water and toluene as hemolytic agents. A 0.1 c.c. of this solution was exposed to 1.6 c.c. of N/12 NaOH. After the mixture had reacted for exactly one minute at 20° C., 3.4 c.c. of a reagent which stops the reaction was introduced. The latter reagent was prepared by adding 1 c.c. of 10N HCl to 400 c.c. of half saturated $(NH_4)_2SO_4$. The final mixture was immediately filtered and the hemoglobin concentration of the filtrate was determined spectrophotometrically. The percentage of undenatured hemoglobin was then calculated.

The hemoglobin from the blood of twenty children with moderate to severe cyanotic heart disease was studied for the rate of alkali denaturation. Blood was also obtained from eight newborn infants and twenty-seven normal older children and adults for comparison.

TABLE III. ALKALI DENATURATION OF HEMOGLOBIN FROM CHILDREN WITH CYANOTIC HEART DISEASE

NAME	AGE	DIAGNOSIS	% UNDENATURED HEMOGLOBIN
B. H.	1 mo.	Tetrad	49*
D. K.	4 mo.	Tetrad	6
C. B.	12 mo.	Tetrad	5
D. S.	13 mo.	Tetrad	5
D. G.	18 mo.	Tetrad	3
D. G.	2 yr.	Tetrad	7
M. R.	2 yr.	Tricuspid atresia	6
R. W.	3 yr.	Tetrad & P.D.A.	4
S. C.	3 yr.	Tetrad	7
D. C.	3 yr.	Tetrad	5
R. R.	4 yr.	Transposition	6
J. P.	4 yr.	Transposition	6
N. B.	6 yr.	Tetrad	11
M. R.	6 yr.	P.S. & I.A.D.	5
R. F.	11 yr.	P.S. & I.A.D.	9
M. S.	14 yr.	Tetrad	4
E. S.	15 yr.	Tetrad	11
R. L.	18 yr.	Eisenmenger	8
D. M.	18 yr.	Tetrad	3
M. N.	30 yr.	Eisenmenger	6
			Mean = 6

*Excluded from calculated mean because of age of patient.
P.S. = Pulmonary stenosis.
I.A.D. = Interatrial defect.
P.D.A. = Patent ductus arteriosus.

RESULTS OF DENATURATION STUDIES

The result of the denaturation studies on the twenty children with cyanotic heart disease can be seen in Table

III. The ages ranged from 1 month to 30 years. Excluding the value from the infant B. H., who was 1 month of age, the range of per cent undenaturated hemoglobin was from 3 to 11 with a mean value of 6 per cent. The one value on the infant B. H. was not included in arriving at the mean since it was anticipated from Singer's work that the infant would have fetal hemoglobin because of its age. The results obtained from the children with cyanotic heart disease are compared with those obtained from the normal children and adults and from the newborn infants in Table IV. It can readily be seen that the hemoglobin from the newborn infants was markedly resistant, whereas that from the cyanotic children was similar to that from the normal children and adults.

Table IV. Hemoglobin Alkali Denaturation Values in Different Conditions

GROUP	NUMBER OF OBSERVATIONS	AGE RANGE	RANGE OF % UNDENATURED HEMOGLOBIN	MEAN % UNDENATURED HEMOGLOBIN
Normal	27	4-70 yr.	3-8	5.0
Newborn	8	—	7-90	63
Cyanotic heart disease	20	1 mo. to 30 yr.	3-11	6.0

DISCUSSION

Residents of high altitude usually exhibit an increase in the hemoglobin content of the blood.[12] In contrast to these observations, however, an increase in the hemoglobin content of the blood was seldom observed in patients with pulmonary emphysema.[3] It has been recognized that patients with cyanotic heart disease regularly develop polycythemia.[13, 14] Our studies show that this polycythemia is for the most part not associated with any changes in the red cell size, fragility, or carbonic anhydrase content. There was no significant increase in the number of reticulocytes in the peripheral blood. However, a very definite decrease in the number of circulating platelets was observed; sometimes they were as low as 10,000 per cubic millimeter. This decrease in platelets in patients with cyanotic heart disease is in contrast to the normal or slightly increased number of platelets found in patients living at high altitude.[15] Bone marrow studies by us in such cyanotic patients did not reveal any abnormal findings except for one patient, D. C., who appeared to have a reduction in the number of megakaryocytes.

Studies by others have shown that adult and fetal hemoglobin differ electrophoretically,[11, 16] spectrophotometrically,[11] by their rates of alkali denaturation,[10, 17-20] by their amino acid composition[21, 22] immunologically,[23] and by crystallography.[24] Andersch and associates[16] reported differences in their sedimentation rate constants, but these were not confirmed by Taylor and Swarm.[25]

In our studies we attempted to ascertain whether or not the hemoglobin from children with cyanotic heart disease is fetal or adult in character. From the results after alkali denaturation, it would appear that the hemoglobin from such patients is *adult rather than fetal* in character. The only exception to this statement would be those patients with cyanotic heart disease occurring early in infancy, where it is expected that fetal hemoglobin would normally be present.[10]

Although the fetus, the person living at high altitude, and the patient with cyanotic heart disease, all have in common, anoxemia, the response of the hematopoietic system is somewhat different in each. These studies eliminate the possibility of the adaptive mechanism in patients with cyanotic heart disease being due to fetal hemoglobin. The value in having a reduced number of platelets in patients with cyanotic heart disease with marked polycythemia is obvious. It is not clear, however, what the mechanism is that accounts for the reduction in the platelets.

SUMMARY

1. In studying the physiologic effects of anoxia in children with cyanotic heart disease, the hematopoietic system has been investigated.

2. Our studies show that the polycythemia in such children is for the most part not associated with any changes in the red cell size, the fragility, or the carbonic anhydrase content. There was no significant increase in the reticulocytes, but a significant decrease in the number of platelets was found. This decrease, however, was not associated with any changes in the bone marrow.

3. From the alkali denaturation tests on the hemoglobin from such cyanotic children, it would appear that the hemoglobin is adult rather than fetal in character.

4. The response of the hematopoietic system to anoxia is somewhat different in the fetus, in the person living at high altitude, and in the patient with cyanotic heart disease.

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CHRONIC FRIEDLÄNDER PNEUMONIA IN INFANCY

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RECENTLY, we have had the opportunity to observe two siblings with lung disease of several years' duration. One is a proved case of Friedländer* pneumonia. In the other, though the clinical course and pathological findings were in keeping with such a diagnosis, no specific etiology was determined. This case exemplifies how the use of antibiotics and chemotherapy prior to or without bacterial investigation can obscure etiology.

A recognized cause of chronic lung disease in adults is the Friedländer bacillus. This etiology is seldom considered in pediatries. These cases are presented in detail with the purpose of stressing the possibility of chronic Friedländer pneumonia in any long-standing nontubercular lung disease in childhood.

Acute primary Friedländer pneumonia is found almost exclusively in the very young and the middle-aged. Two-thirds of the adult cases have occurred in the fifth and sixth decades of life. Of the twenty-eight cases reported in children, all have occurred in infants less than 15 months of age.

Prior to the advent of sulfonamides and antibiotics, acute Friedländer pneumonia in adults ran a rapidly fatal course. In Solomon's[1] original series (thirty-two cases), the mortality was 97 per cent; the average day of death, the sixth or seventh. In a recent excellent review of Friedländer-Aerogenes infections in children, Obrinsky and associates[2] found that the disease in infancy was more benign. Before the introduction of sulfonamides the average mortality in children was 41 per cent. All patients reported since have recovered with the use of sulfadiazine and/or antibiotics.

In adults, about one-third of the acute cases pass into a chronic phase of pulmonary necrosis and cavity formation. Since gross necrosis with sloughing and cavity formation can occur as early as the fourth day of illness (Belk[3]), only those cases should be considered chronic in which signs and symptoms last more than four weeks.

The incidence of chronic Friedländer pneumonia in adults is low. To date, there are fewer than 100 reported cases. The largest series comprised seventeen patients reported by Solomon[4] in 1940, at which time he stated that no case of chronic pulmonary infection due to Friedländer bacillus had ever been observed in childhood. Miller's[5] case of Friedländer pneumonia, beginning in a 3-week-old infant, could be classified as chronic, roentgenographic evidence of pulmonary cavitation being present two months after the onset of illness.

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*The close similarity of Friedländer bacillus and *Aerobacter aerogenes* is well established. Throughout the body of this report, the synonyms, *Bacillus mucosus capsulatus*, *Klebsiella pneumoniae*, and *Bacillus lactis aerogenes*, are retained as they appeared in the original references.

CASE REPORTS

CASE 1.—R. H., 3½-month white male, first admitted to the St. Louis Children's Hospital Dec. 3, 1947, because of diarrhea since birth. One month prior to admission, the parents noticed abdominal enlargement. One week before admission he developed cough with high fever and was hospitalized. A diagnosis of pneumonia was verified by x-ray, and penicillin was administered. Abdominal paracentesis had revealed white-flecked serosanguineous fluid. The family history was relevant in that the father, while in the Army, was told that he had "spots" in his lung. A 4-year-old female sibling had had a nonproductive cough for two years. Recent chest films of the father and this child were reported as negative.

Physical examination revealed an acutely ill, dehydrated infant. The lungs were clear except for high-pitched breath sounds posteriorly. The abdomen was protuberant with shifting dullness in the flanks. The liver edge was palpable two fingerbreadths below the costal margin.

Clinical course: On admission, abdominal paracentesis yielded 75 c.c. of serosanguineous fluid. Stained smears showed numerous diplococci, but cultures were negative. Following routine cultures, subsequently reported as sterile, the patient was started on penicillin and streptomycin. During the first two weeks, diarrhea and dehydration were severe. Repeated stool examinations were negative for nonlactose fermenters, ova, parasites, and eosinophils. Proctoscopy revealed mucopurulent exudate but no ulceration. By December 18, the diarrhea was controlled and antibiotics discontinued. On December 21, the temperature rose to 38.6° C. The white blood count was 31,200 with a left shift. Physical examination was negative. Penicillin therapy was resumed and triple sulfonamides added. Five days later a subcutaneous abscess was detected at the site of a penicillin injection in the left thigh. Following incision and drainage, the temperature fell promptly, but leukocytosis persisted. X-rays of the involved extremity were normal.

Chest films the day after admission showed haziness over the entire right lung field with patchy areas of pneumonic infiltration. Physical examination of the chest was normal. Several tuberculin, histoplasmin, and coccidiomycin skin tests were negative. Gastric washings on ten occasions were negative for tubercle bacilli. Tryptic activity of the duodenal secretions was normal. Chest films three weeks later (December 29) revealed consolidation in the right upper lobe and a small area of pneumonic infiltration in the left upper lobe. On December 31, laryngoscopy was performed. Tracheal secretions yielded a pure growth of *B. mucosus capsulatus* sensitive to 2 to 5 μg per cubic centimeter streptomycin and to less than 10 mg. per cent sulfadiazine. Accordingly, streptomycin was restarted.

On Jan. 10, 1948, breath sounds were diminished over the left chest. Repeat x-rays showed minimal patchy pneumonic infiltration in the left upper lobe. The pneumonic consolidation in the right upper lobe was improved. Laryngoscopy was repeated on January 19. The tracheal mucosa appeared red with a moderate amount of secretion. Cultures were negative. The child's condition improved, and streptomycin was discontinued on January 26. One week later, sulfonamides were discontinued. Chest films at this time showed clearing on the left, but the right lung was unchanged.

On discontinuation of medication, the patient developed respiratory difficulty with wheezing and suprasternal retraction. Fluoroscopy suggested cavity formation in the right upper lobe. Clinically, the child continued to do well with daily weight gain, normal temperature and white blood count. He was discharged on Feb. 21, 1948. X-rays taken at this time were unchanged.

Second Admission (July 22, 1950): Following discharge, the patient had a persistent cough and frequent bouts of

fever. In October, 1949, he developed an infection of his toe which required hospitalization. Two months later an abscess was detected over the sacrum. This was incised but had continued to drain.

Physical examination: The infant appeared chronically ill. The oral mucosa was covered with spotty white exudate. Resonance and breath sounds were impaired over the left upper anterior chest and the right middle chest posteriorly. Both liver and spleen were palpated three finger-breadths below the costal margin. Over the sacrum a small indurated area exuded purulent, foul-smelling secretion.

Laboratory data: Hemoglobin was 8.3 Gm., red blood count 5.23 million, white blood count 3,600, 52 segmentals, 46 lymphocytes, 2 monocytes. All subsequent white blood counts were elevated with a relatively normal differential. Repeat skin tests were negative. An admission throat culture yielded *Streptococcus viridans* and hemolytic *Staphylococcus aureus*. Studies relating to liver function were: Total protein 6.9 Gm., albumin 3.86 Gm., globulin 3.04 Gm. The cephalin flocculation was + in 24 hours, ++ in 48 hours. On three occasions, Friedländer bacillus and *Staph. aureus* were isolated from the sacral sinus tract. Eleven gastric washings were negative for acid-fast and Friedländer bacilli.

Chest x-rays revealed no appreciable change from previous films. The lumbosacral spine was negative.

Course: Penicillin was started on admission. Repeat bronchoscopy revealed mucosal injection and exudate on the right with negative cultures. Sensitivity studies on the organisms isolated from the sinus tract were: *B. mucosus capsulatus* inhibited by 0.5 μg per cubic centimeter aureomycin, 0.1 μg per cubic centimeter dihydrostreptomycin, 5.0 μg per cubic centimeter polymixin B, 2 μg per cubic centimeter Choloromycetin, and 5 μg per cubic centimeter terramycin. *Staph. aureus* inhibited by 0.5 μg per cubic centimeter penicillin, 0.5 μg per cubic centimeter dihydrostreptomycin, and no inhibition by 10 μg per cubic centimeter polymixin B. Accordingly, aureomycin and dihydrostreptomycin were added to therapy. The sacral sinus healed rapidly, but there was no evident effect on the pulmonary pathology. The temperature curve showed a progressive rise with daily elevations to 39° C. in the last week of hospitalization. He was discharged on Sept. 2, 1950, on aureomycin prophylaxis, 250 mg. twice daily.

Third Admission (Jan. 14, 1951): The patient was now 3 years 5 months of age. Since discharge in September, 1950, his condition had become progressively worse with unrelenting cough, dyspnea, and daily temperature elevation.

Physical examination: The child appeared pale and malnourished. There was no cyanosis or respiratory distress. Clubbing of the digits was marked. Fine râles were heard at both lung bases. Liver and spleen were enlarged to the level of the umbilicus.

Laboratory data: Repeat nose and throat, blood, stool, and urine cultures were negative for Friedländer bacillus. Total protein was 6.65 Gm., albumin 3.35 Gm., globulin 3.30 Gm. Cephalin cholesterol flocculation was +++ in 24 hours, ++++ in 48 hours, thymol turbidity +++.

Clinical course: Dihydrostreptomycin, penicillin, and Chloromycetin were started soon after admission. The temperature remained elevated with daily spikes to 39.4° C. Respiratory distress marked a rapidly downhill course. The patient expired Jan. 23, 1951.

Autopsy performed by Dr. James C. Roberts.

Thorax: Gross pathology: The tracheobronchial and mediastinal lymph nodes were enlarged two to ten times. Adhesions obliterated the pleural cavity completely on the right, focally on the left. The lungs were acrepitant and cut with resistance. Both upper lobes contained numerous thin-walled cavities, 0.5 to 1.5 cm. in diameter, communicating with bronchi.

The lower lobes showed an almost confluent fibrosis. Bronchi were dilated throughout.

Lungs: Microscopic pathology: In the upper lobes there were broad bands of connective tissue containing large mononuclear cells, plasma cells, lymphocytes, and a few polymorphonuclear leukocytes. Many alveolar spaces were lined with cuboidal epithelium and syncytial giant cells. Large multinucleated giant cells were also seen free in the alveoli. Some of these were similar to those attached to the alveolar wall; others had the characteristics of foreign body giant cells. The alveolar walls were thickened by varying amounts of connective tissue consisting of loosely arranged collagen fibers and fibroblasts. A large bronchiectatic cavity was lined with connective tissue and at one point by metaplastic squamous epithelium. In the left upper lobe was a necrotic focus surrounded by vascular granulation tissue. Foreign body giant cells were seen in close relation to this focus. In the right upper lobe were numerous small abscesses with many polymorphonuclear leukocytes surrounded by fibroblasts, a few mononuclears, and foreign body giant cells. Nonseptate branching hyphae were scattered through these necrotic foci. It was the opinion of the mycologist that these represented a species of Mucor. In both lower lobes, syncytial giant cells, apparently arising from the lining, were lying free in the alveoli. A few of these contained eosinophilic cytoplasmic inclusions. Some of the nuclei showed clear central inclusions which occupied about one-third of the nucleus. Many alveoli contained an exudate of fibrin, mononuclear cells, polymorphonuclear leukocytes, and eosinophilic debris. In others, the exudate was organized or necrotic. A few contained only edema fluid lined by acellular hyaline membranes. In all of the lobes of the right lung there were small granulomas, two to five per section, composed entirely of epithelioid cells.

Liver: Weight 699 grams. Capsular adhesions were present. The parenchyma appeared slightly yellow, and the central areas were a red purple.

Microscopically, there was centrolobular vascular congestion and leukostasis. Portal lymphocytosis with an increase in portal fibrous tissue was noted.

It was the pathologist's opinion that there was more than one causal agent involved. The extensive peritrunkal fibrosis, fibrosis of the interlobular septa in all lobes, and the bronchiectasis were of long duration. These changes were interpreted as part of the primary disease, the etiology of which could not be determined on the basis of the anatomic study. The proliferation of connective tissue in the alveolar walls, present in all lobes of the lungs, could have been a part of the primary disease. However, there appeared to be an active disease process. The syncytial giant cells (interpreted by Dr. Henry Pinkerton as the lesion of Hecht giant cell pneumonia) and alveolar cellular exudate were considered as Hecht giant cell pneumonia. The latter was believed to be of comparatively recent origin, not more than a few months' duration. *Staph. aureus* was cultured from the lungs and trachea, and an occasional coccus was present in the bronchial and alveolar exudate. This organism may have played a terminal role in the more acute part of the pneumonic process, most prominent in the lower lobes. Fungi, associated with definite lesions, were present only in the upper lobes of the lungs. The fungal infection was likewise interpreted as a secondary process superimposed on the primary disease. The etiology of the small isolated epithelioid granulomas seen only in the right lung was not apparent. No organisms were stained within these lesions.

No fungi, acid-fast bacilli, or other organisms were found in the caseous node adjacent to the left upper lobe, and no primary tuberculous lesion was identified in the lung tissue. The only lesions elsewhere in the body that may have been related to those in the lung were the nodular fibrous scars in the

mesenteric lymph nodes, the fibrous adhesions in the body cavities, and the few small focal lesions in a tracheobronchial node.

CASE 2.—J. H., 8 months of age, younger brother of R. H., was first seen at the St. Louis Children's Hospital on Oct. 19, 1949. Since the age of one week he had had a recurrent papulopustular skin eruption. Therapy was varied and included penicillin injections. Three months prior to admission he developed fever, oral lesions, cough, vomiting, and diarrhea. On penicillin therapy, the stomatitis improved, but he continued to have fever, cough, and diarrhea. Failing to improve on the addition of aureomycin, he was transferred here.

Physical examination revealed a chronically ill infant. There was a pustular eruption over the back with many small clear vesicles. Over the pubic and inguinal regions the lesions were maculopapular. There was mild generalized lymph node enlargement. In the right upper chest, resonance was impaired and breath sounds diminished. Liver and spleen were below the costal margin three and one finger-breadths, respectively.

Laboratory data: Kline, tuberculin, and histoplasmin skin tests were negative. The cephalin flocculation was ++ after 48 hours. Throat culture on November 1 grew a *Staph. albus*. Gastric washings failed to reveal tubercle bacilli. Stool specimens showed tryptic activity. Chest x-rays revealed an area of consolidation in the right upper lobe with heavy bronchovascular markings in the right lower and middle portions of the lung.

Course: On penicillin therapy, the temperature remained normal for one week, at which time there was an elevation to 39.4° C. Examination revealed bilateral otitis media and rhinopharyngitis. Aureomycin was added, and within twenty-four hours the temperature was normal. He remained on these antibiotics for two weeks with gradual clinical improvement. Chest films at the time of discharge (Nov. 13, 1949) showed no essential change in the right lung.

Second Admission (Jan. 24, 1950): Two weeks after discharge a "tonsil abscess" appeared on the right side of the neck. There was prompt subsidence of the swelling with aureomycin therapy. Except for a persistent cough and the recurring skin rash, he continued to do well. Four days prior to admission the parents noticed marked abdominal distention.

Physical examination: Temperature was 39.2° C. The patient was markedly dyspneic and had a harsh dry cough. Over the neck, trunk, and buttocks was a diffuse papular rash with a greasy yellow crust. There was moderate generalized lymph node enlargement. Auscultation of the chest revealed harsh breath sounds bilaterally. The abdomen was distended and tympanitic. Palpation of viscera was not possible.

Laboratory data: Significant blood chemical analyses: Cholesterol 65 mg. per 100 ml., total protein 6.67 Gm., albumin 3.45 Gm., globulin 3.22 Gm. The cephalin flocculation was ++ in 24 hours and +++ in 48 hours. A pure growth of *Str. viridans* was cultured from the throat on admission. Numerous sputum examinations were negative for tubercle bacilli. X-rays of the chest showed some clearing of the previously noted infiltration in the right upper lung.

Course: During the first week the child received penicillin and streptomycin parenterally. On discharge (Feb. 14, 1950) the skin was clear, but the abdominal distention and lung pathology were unchanged.

Third Admission (May 19, 1950): One month before admission an abscess had appeared in the left groin and was incised by his physician. About the same time he developed "flu" and "double pneumonia." He was hospitalized and, failing to improve, was referred back to St. Louis Children's Hospital.

Physical examination: No cyanosis was evident, but he appeared quite dyspneic. There was suggestive clubbing of fingers and toes. The skin was

clear. In the left inguinal region was a large node with an apparently healed sinus of the overlying skin. There was dullness to percussion and tubular breath sounds over the lower half of the right chest anteriorly and posteriorly. The liver was enlarged three fingerbreadths, and the spleen was one fingerbreadth below the costal margin.

Laboratory data: Hemoglobin was 8 Gm., red blood count 4.3 million, white blood count 19,200, 9 stabs, 29 segmentals, 62 lymphocytes. Total protein was 7.19 Gm. per 100 ml., albumin 3.94 Gm., globulin 3.25 Gm., serum cholesterol 125 mg. Cephalin flocculation was normal. Repeated skin tests were negative. An admission chest film showed "increased density involving most of the right lung. It is not possible to exclude encapsulated fluid."

Course: Despite aureomycin, the patient continued to run a low-grade fever. On May 23, a right thoracentesis was performed, yielding 10 c.c. of sterile serosanguineous fluid. One week after admission a draining sinus was detected at the site of the original inguinal abscess. Cultures were taken with no growth.

In the hope of discovering the etiology of this chronic disease process and to promote adequate drainage, the abscess, sinus tract, and regional lymph node were removed on June 15.

On June 24, bronchoscopy was performed with great difficulty because of the small size of the trachea. The right bronchus was hyperemic and smaller than the left. Considering the failure of pulmonary resolution and to prevent involvement of the left lung, exploratory thoracotomy seemed warranted (July 20). The entire right lung was involved, necessitating pneumonectomy. The postoperative course was uneventful.

The patient was discharged on the thirty-sixth postoperative day (Aug. 24, 1950). The liver and spleen had not regressed.

Fourth Admission: The patient was readmitted on Sept. 12, 1950, because "he was not doing well." Shortly after discharge, the skin rash reappeared, and the glands in his neck became swollen. The parents gave the patient eight to ten capsules of aureomycin (250 mg.) with some improvement. Because of cough and rapidly increasing dyspnea, he was brought back to the St. Louis Children's Hospital.

Physical examination. On admission, the respirations were rapid, but there was no cyanosis. There was evident clubbing of the fingers and toes. The trachea was deviated sharply to the right, and there was moderate suprasternal retraction. The right chest was sunken with diminished respiratory excursions, dullness on percussion, and absent breath sounds. Expiratory rhonchi were heard on the left. The liver was enlarged 5 cm. and the spleen 2 cm. below the costal margin.

Laboratory data: Total protein was 7.31 Gm. per 100 ml., albumin 3.99 Gm., globulin 3.32 Gm. Admission nose and throat culture grew *Staph. albus.* Chest x-rays showed mediastinal shift to the right.

Course: Aureomycin was started in therapeutic doses. Four days after admission a small cutaneous abscess on the right leg was detected. This was aspirated and cultured without growth. There was progressive improvement, and he was discharged Oct. 3, 1950, on aureomycin prophylaxis, 50 mg. twice daily.

Fifth Admission: J. H. was readmitted Nov. 22, 1950, because of abdominal distention, persistent cough, and expectoration.

Physical examination: The patient, now 21 months of age, was in mild respiratory distress with slight inspiratory retraction. The lung findings were essentially unchanged. The abdomen was tremendously distended with shifting dullness on percussion.

Laboratory studies: Total protein was 6.32 Gm. per 100 ml., albumin 3.56 Gm., globulin 2.76 Gm. X-rays of the chest were unchanged since the last examination.

Course: Penicillin, streptomycin, and aureomycin were ordered on ad-

mission. He appeared to be recovering from his acute respiratory illness when on November 27 at 10: 30 A.M. while having his temperature taken, he suddenly gagged, coughed, and developed severe respiratory difficulty. Cyanosis was intense. Examination revealed poor air exchanged over the left chest. Laryngoscopy was performed, and a moderate amount of mucus was obtained with some improvement. He was placed in oxygen. Adrenalin was without effect in relieving the audible wheezing. Digitalization was started at 12:15 P.M. Because of alarming respiratory distress, at 12:30 P.M. bronchoscopy was performed. The procedure was difficult because of the marked angulation of the trachea to the right. To promote adequate drainage, it was considered best to perform a tracheotomy. Despite all measures the patient expired at 1:50 P.M.

Examination of Surgical Specimens.—

Right lung: In the apex of the right lower lobe there was an abscess 4 cm. in diameter without a well-defined fibrous wall and filled with cheesy gelatinous material. Microscopically, normal lung parenchyma was replaced by fibrosis, cellular inflammatory tissue, and granulomas (single, grouped, or solid sheets). The latter consisted of loosely arranged epithelioid cells with an occasional giant cell. Larger granulomas with necrotic centers were frequently surrounded by a narrow zone of lymphocytes and mononuclear cells. The bronchial branches were moderately dilated and surrounded by round cells, especially in the lower lobe.

Inguinal lymph node: The normal architecture of the lymphoid tissue contained a number of large granulomas with necrotic centers surrounded by a collar of epithelioid and mononuclear cells. No caseation or giant cells were seen. Smears and cultures of both surgical specimens were negative.

Autopsy performed by Dr. Dale Schulz.

Thorax: Gross pathology: The mediastinum was deviated sharply to the right. Mediastinal lymph nodes appeared normal. The right pleural cavity was obliterated by fibrous adhesions. The left lung weighed 392 grams and was subcrepitant. The pleura appeared normal. The cut surface yielded pink frothy fluid with no gross lesions.

Microscopic pathology: The architecture of the lung was well maintained. The alveolar walls and septa appeared thickened and edematous. Several small, clearly demarcated granulomas were present with fibrous walls infiltrated by mononuclear cells. A few granulomas contained, centerally, large ovoid cells with vesicular oval nuclei with one resembling a large Langhans' type giant cells. Others contained coalescing broken cells.

Liver: Weight 533 grams. One rather large diffuse focus of mixed mononuclear infiltrate with a suggestion of granuloma formation and necrosis was seen.

Peritoneum: There was a chronic granulomatous peritonitis with a fibrinopurulent exudate.

Mesenteric lymph node: At the ileocecal junction a greatly enlarged (2 × 2.5 cm.) lymph node contained a sharply delimited mass of white caseous material which had ruptured into the peritoneal cavity. Microscopically, this node showed a normal architecture at one end. At the other end the pattern was obliterated by cellular fibrous tissue containing foci of lymphocytes which gradually frayed out into a loose disarranged collection of large pale cells with copious cytoplasm. No granulomas were seen. A section of another mesenteric lymph node was normal histologically.

DISCUSSION

It is well to remember that the natural course of this disease has undoubtedly been modified by specific therapy.

Source of Infection.—There is a striking association of vomiting and diarrhea with pulmonary Friedländer infections in infancy. Whereas so-

called "parenteral" diarrhea is common in children, it is possible that the diarrhea is primary with secondary lung involvement. Baehr and associates[6] feel strongly that the Friedländer group of organisms is most frequently found associated with infections of the gastrointestinal, genitourinary, and biliary tracts. They regard pulmonary involvement as secondary to some such focus.

In a study of fecal flora by Dudgeon,[7] the mucosus capsulatus group occurred in 5.5 per cent of the cases. These organisms were found most commonly in association with abnormal conditions of the intestinal tract. Hay[8] found these organisms present in 13 per cent of normal stools and twice that value under diarrheal conditions.

There are several reported epidemics of diarrhea due to the Friedländer-Aerogenes organisms. In 1932, Jampolis and co-workers[9] reported a series of twenty-two newborn infants with enteritis caused by *B. mucosus capsulatus*. The source of infection was traced to three nursemaids who harbored the organism in almost pure culture in the throat and stool. A few of the affected infants developed terminal bronchopneumonia and otitis media, yielding *B. mucosus capsulatus* on culture.

In 1941, Cass[10] reported five cases of diarrhea in a newborn nursery, due to *B. lactis aerogenes*. Two were complicated by septicemia.

Walcher[11] in 1946 reported an epidemic of diarrhea in eighteen infants less than 10 months of age. All had positive stool cultures for *B. mucosus capsulatus*. Repeat cultures during convalescence were negative. A subsequent study, by the same author, of stool cultures in infants less than one year of age, revealed only two positive *B. mucosus capsulatus* cultures from 107 patients. These infants were asymptomatic.

Of interest in this aspect of the disease is the high incidence of diarrhea in cases of Friedländer septicemia. This is particularly striking in the newborn and premature infants. In Obrinsky's[2] series of five cases of Friedländer septicemia in the neonatal period, two had severe pre-existing diarrhea. A third case was complicated by congenital atresia of the colon, necessitating bowel resection. It seems probable that the Friedländer septicemia may have been caused by manipulation of the involved bowel.

In five of the six autopsies of Jampolis'[9] series, *B. mucosus capsulatus* was cultured from the heart's blood.

Such reports strongly suggest that in infancy Friedländer pneumonia may well be secondary to enteral infection.

In Case 1, diarrhea was present since birth and constituted the major problem during the first few weeks. A logical sequence could have been enteritis, blood stream infection, and finally lung involvement. Such a supposition is unnecessary in Case 2, infection probably being air-borne by close contact.

Temperature.—Considering the extent of lung involvement and extrapulmonary suppurative complications, both children ran a relatively afebrile course with only an occasional temperature elevation. During the last few weeks of life, Case 1, R. H., had a septic temperature course with daily spikes to 39° to 40° C.

Blood Cell Change.—Serial blood count determinations were made in both cases. On several admissions both children showed a hypochromic anemia. The white count ranged from 3,600 to

31,900. However, of twenty-eight counts, only four were less than 10,000. On the whole, the counts were lower in Case 2. In Case 1, except for one count of 3,600, all were over 15,000 with a slight increase in polymorphonuclears. Despite leukocytosis, neither child showed more than a minimal shift to the left in the Schilling index. In Case 1 on only five occasions were the stabs increased beyond 6 per cent and always less than 15 per cent. In Case 2 in four counts the stabs were increased from 6 to 10 per cent only. These findings are unusual in the light of severe pulmonary involvement.

Signs and Symptoms.—No respiratory symptoms were recorded during the first three weeks of hospitalization in Case 1. With this exception, there was a dry hacking cough throughout the illness in both cases. Abnormal physical findings in the chest were minimal. On occasions there were diminished resonance and breath sounds over involved lung areas. Terminally, fine râles were present in Case 1.

Duration of Illness.—In chronic Friedländer pneumonia, cavitation, bronchiectasis, and fibrosis may persist for years. During exacerbations the pathological process is repeated with progressive lung involvement. It is in this stage that the disease simulates pulmonary tuberculosis and not infrequently is misdiagnosed as such.

In Solomon's series[4] the duration of illness was from one month to three years. Brulé's[12] patient suffered exacerbations and remissions over a nine-year period with ultimate death.

Death terminated the illness thirty-seven months after onset of illness in Case 1 and sixteen months after onset in Case 2.

X-ray Findings.—Kornblum[13] and his co-workers describe a sequence of pathological events in Friedländer pneumonia as evidenced by serial roentgenograms. During the acute phase there is a patchy bronchopneumonic infiltration followed by coalescence to give the picture of pseudolobar consolidation. To quote: "The predominant finding is a massive, dense, usually homogenous shadow, which was frequently suggestive of fluid." The next stage consists of pulmonary necrosis with the formation of abscesses and numerous thin-walled cavities. Finally, there are fibrosis and healing. This sequence is not fixed. Complete resolution of the consolidated areas can take place without the formation of abscess cavities. Such was the case in all of Grotts'[14] patients. Likewise, there may be complete resolution of lung abscesses.

Several x-ray reports in our cases were worded almost identically with Kornblum's[13] classical description: "patchy pneumonic infiltration, . . . not possible to exclude encapsulated fluid."

In Case 1, the x-ray findings over a three-year period revealed little significant change from the onset of illness to demise.

Hepatic Dysfunction.—In adults, frequent mention is made of the association of Friedländer infection and cirrhosis of the liver. Of the thirteen autopsies in Hyde's[15] series of acute Friedländer pneumonia, portal cirrhosis was present in four patients (31 per cent) and fatty liver in five patients (38 per cent). He compared these percentages with Spain's[16] findings—portal cirrhosis being present in only 6 per cent of more than 3,000 autopsies at the Bellevue Hospital. Since 88 per

cent of Hyde's patients were over 40 years of age, and most were males, the possibility of chronic alcoholism as a causal factor cannot be excluded. In Solomon's[4] series of chronic Friedländer pneumonia, alcoholism was recorded as a possible "predisposing factor" in nine out of seventeen patients. All three of his cases with clinical evidence of liver involvement gave a history of alcoholism, and in one a diagnosis of cirrhosis had been made four years previously.

Both of our patients exhibited clinical and laboratory evidence of hepatic dysfunction. Case 1 was admitted with hepatomegaly and ascites. The total protein was low with a normal albumin-globulin ratio. On the second admission the spleen was also palpable, and the globulin was elevated. Terminally, the total protein was 6.65 Gm. per 100 ml., albumin 3.35, globulin 3.30 Gm.; cephalin flocculation was +++ in 24 hours and ++++ in 48 hours; thymol turbidity +++.

Case 2 was admitted with an enlarged liver. On the following admission there was an elevation of the globulin, and the cephalin flocculation was ++ and +++ in 24 and 48 hours, respectively. These values were essentially unchanged up till pneumonectomy. Four months later there was a significant drop in the total protein from 7.3 to 6.3 Gm., and a fall in globulin from 3.32 to 2.76 Gm. These findings were not accompanied by change in liver size.

Obviously, in these two cases some explanation other than chronic alcoholism must be offered for the association of hepatic disease and Friedländer pneumonia.

Complications.—Both cases showed classical pulmonary complications. Pulmonary cavitation, abscess formation, and fibrosis were demonstrated by fluoroscopy and/or x-ray and proved by operation and autopsy. In Case 1 a small sterile pleural effusion was present on the third hospital admission. The relation of the suppurative nodes in the neck and groin in Case 2 to the original infection is not known since the cultures were nonrevealing. Case 1 developed a draining sacral sinus yielding Friedländer bacillus on culture two years after the onset of illness.

Treatment.—The value of the different sulfonamides in acute Friedländer infections is unpredictable and can be determined only by in vitro sensitivity studies.

In 1945, Anderson[17] reported that penicillin was ineffective against *K. pneumoniae* in vitro. Not only has this been substantiated clinically, but several authors, notably Nataro and associates[18] and Gill,[19] have found that on penicillin alone their patients were made worse.

Following Heilman's[20] studies on the sensitivity of micro-organisms of the Friedländer group to streptomycin, there have been a number of reports of recovery from acute Friedländer pneumonia in infants and adults by the use of this drug.

More recently, aureomycin has been successfully used in the treatment of acute Friedländer pneumonia.

The Friedländer bacillus has been found to be sensitive to terramycin in vitro, and experimental data suggest its future clinical value.

No clinical reports pertaining to the efficacy of Chloromycetin against this organism have been available to date.

Early in the acute phase of Friedländer pneumonia broad coverage with

the appropriate antibiotic and chemotherapeutic agents as determined by in vitro sensitivity studies is highly desirable. Once the patients have developed extensive pulmonary necrosis with cavitation, the value of these drugs is greatly limited.

The treatment of chronic Friedländer pneumonia offers a difficult problem. Early authors felt that therapy in these cases should be conservative and surgical intervention best avoided. Four of Solomon's ten patients with chronic lung abscess received surgical drainage by thoracotomy. One of these patients died, and the other three continued to show persistent abscess cavities. In two patients, chronically draining thoracic fistulas were a troublesome complication. Of the six who received nonsurgical care, one died, one was "cured," and four recovered with persistent lung abscesses. The results were thus comparable in the two groups except for the complication of draining thoracic fistulas in some of the operated group. Hyde and Hyde[15] also felt that the treatment of choice for the chronic cases was conservative. Most recently, Wylie and Kirschner[21] have reported a series of sixteen patients with Friedländer pneumonia. Eight of these patients received drainage of the pulmonary abscesses by thoracotomy during the acute phase. All continued to show chronic lung disease, often with persistent bronchopleural cutaneous fistulas and subsequently required further surgery in the form of lobectomy, pneumonectomy, or muscle plasty. There were two post-operative deaths in this group due to Friedländer pneumonia of the previously uninvolved lung six months and five years, respectively, after the original onset. Pulmonary resection was performed in three patients without previous drainage with uneventful recovery.

Analyzing these reports, the value or wisdom of draining the acute lung abscess due to Friedländer bacillus appears doubtful. On the other hand, pulmonary resection during the chronic phase would seem to offer the only hope for recovery. Without surgical excision of the involved areas there is the constant threat of reactivation of the disease process with involvement of lung tissue previously unaffected. Such was the case of R. H. who, at the time surgery was considered, had extensive bilateral inoperable lung pathology. Another complication, seen not infrequently in adults, is the development or reactivation of pulmonary tuberculosis. In Wylie's[21] series of five patients not treated surgically, three developed active tuberculosis.

CONCLUSION

To our knowledge, R. H. represents the only reported case of chronic Friedländer pneumonia in infancy. Friedländer bacillus was grown in pure culture from bronchoscopic aspirations five weeks after the onset of illness. Without this fortuitous discovery, the diagnosis could not be made unequivocally despite the classical clinical picture. Futher attempts to isolate the organism from the respiratory tract were unsuccessful. This was anticipated subsequent to the use of reputedly effective sulfonamides and antibiotics.

Almost three years later, Friedländer bacillus and *Staph. aureus* were cultured from a discharging sinus tract in the lumbosacral region. Numerous interim sputum, blood, and gastric cul-

tures were negative for Friedländer organisms.

X-ray findings throughout the three-year course of illness were essentially unchanged from those taken at the time Friedländer bacillus was first isolated from the lung. This strengthens the diagnosis of chronic Friedländer pneumonia in the face of terminal secondary lung infection by *Staph. aureus* and *Mucor mycosis*. The identical nature of disease in the two siblings is assumed by constant exposure, similar clinical and laboratory courses. In the younger sibling, whose disease was of much shorter duration, there was no evidence of either staphylococcic or mycotic involvement of the affected lung.

It was our impression that the giant cell pneumonia, the *Mucor mycosis*, and the *Staph. aureus* pneumonia in Case 1 were terminal infections of not more than a few months' duration. This view was supported by the pathologists. Diffuse chronic fibrosis and bronchiectasis have been described in chronic Friedländer pneumonia. In most pathological reports of chronic Friedländer pneumonia the organism has been isolated by culture. However, all of these reports were prior to the use of specific antibiotics and effective sulfonamides.

Concerning failure to isolate the causative organism in the second case, one must keep in mind the specific therapy administered prior to, during, and between hospital admissions. Serum from this patient one year after the onset of his illness failed to agglutinate the organism cultured from the draining lumbosacral sinus of his affected sibling. Urines for precipitin tests with "A" and "B" Friedländer serum were negative. Such studies do not exclude Friedländer infection. Reflecting on the known exposure, the similar prolonged course of lung disease with characteristic cavitation and diffuse fibrosis, we are considering this case as another example of chronic Friedländer pneumonia.

We wish to thank Mrs. Ruth B. Gerstung and Mrs. Herma Wolf for their technical assistance.

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INTRAVENOUS CHLORAMPHENICOL IN THE TREATMENT OF MENINGITIS DUE TO HEMOPHILUS INFLUENZAE (TYPE B)

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INTRAVENOUS chloramphenicol (Chloromycetin*) used in the treatment of meningitis due to *Hemophilus influenzae* (type B) represents an attempt to provide an effective medication by the route which insures greatest safety and rapidity of administration.

Chloramphenicol has been shown to pass readily from the blood to the spinal fluid, the spinal fluid concentration reaching from 30 to 50 per cent of that found in the blood.[1] Previous reports indicate that chloramphenicol given by mouth or by rectum to patients with meningitis due to *H. influenzae* may surpass any previous form of therapy for this disease.[2, 3] Based upon these findings we have used intravenous chloramphenicol since it was made available to us in January, 1951, in the treatment of meningitis due to *H. influenzae*.

Nine patients with meningitis due to *H. influenzae* were admitted to Riley Hospital in 1951. Of these, three were not treated with intravenous chloramphenicol because of the inability to identify typical organisms on direct smear of the spinal fluid at the time of admission or because of the use of oral chloramphenicol immediately prior to hospitalization.

Treatment of these three patients consisted of either the continuation of oral chloramphenicol or the administration of penicillin and sulfadiazine until a bacteriological diagnosis was made by culture. At that time penicillin and sulfadiazine were discontinued and oral chloramphenicol was started. All patients were treated with 60 mg. per kilogram per twenty-four hours. These patients demonstrated clinical and bacteriological responses which were comparable with those described by other authors. They were considered fully recovered at the time of discharge from the hospital and have continued to do well subsequently.

The remaining six patients were chosen for intravenous chloramphenicol therapy because they had not received chloramphenicol or sulfadiazine prior to admission to the hospital. The youngest patient in this group was one year of age. The oldest was 3 years. Five of the patients had therapy started within forty-eight hours following onset of signs of meningeal irritation. The sixth patient was not brought to the hospital until the sixth day following the onset of meningeal signs. All patients had spinal fluid examinations at the time of admission which showed the characteristic elevation of the cell count, and *H. influenzae* (type B) organisms were identified by a Gram stain of the direct smear and by Neufeld's reaction. Cultures of the

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spinal fluids were confirmatory in all cases. Blood cultures were taken from the six patients at the time of admission. Four were positive for *H. influenzae*.

Immediately following identification of *H. influenzae* organisms on direct smear of the spinal fluid, intravenous chloramphenicol therapy was started in amounts of 50 mg. per kilogram per twenty-four hours in divided doses every six to eight hours. The medication was diluted by adding it slowly and with constant agitation to 100 to 150 c.c. of 5 per cent dextrose in distilled water. It was then introduced into the tubing of an infusion.

The six patients were treated with intravenous chloramphenicol for an average of sixty hours, following which oral chloramphenicol was begun in amounts of 50 mg. per kilogram per twenty-four hours given in divided doses for an average of 8.9 days.

Five of the six patients had repeat spinal fluid cultures following the first twelve hours of intravenous therapy. Four of these cultures were negative. One culture remained positive at twelve hours but was negative following twenty-four hours of therapy. The sixth patient failed to receive a repeat lumbar puncture.

Three of the four patients having positive blood cultures on admission had repeat blood cultures which were negative after twelve and twenty-four hours of intravenous therapy. A repeat blood culture was not obtained on one of the patients who had a positive blood culture on admission.

A satisfactory clinical response as judged by return of temperature to normal and resolution of irritability and somnolence was observed within seventy-two hours of onset of intravenous chloramphenicol therapy in all but two patients. The first of these patients had a persistence of irregular fever and marked irritability until the seventh hospital day, at which time subdural aspiration by means of bilateral posterior frontal trephinations was productive of 4 to 6 c.c. of sterile, xanthochromic fluid bilaterally. Repeat subdural aspirations on the twelfth hospital day yielded 1 to 2 c.c. of sterile, xanthochromic fluid bilaterally. The patient was significantly improved following the first aspiration and ultimately recovered uneventfully. The clinical course of the second patient was complicated by a purulent otitis media from which was cultured a *Staphylococcus aureus*. This patient received penicillin and sulfadiazine in addition to intravenous chloramphenicol during the first thirty-six hours of therapy. The spinal fluid and blood cultures on this patient were negative following the first twelve hours of therapy, although there was a persistence of low-grade fever for the first ten hospital days. This prolonged fever was attributed to the otitis media.

The six patients were discharged in good health with an average hospital stay of sixteen days. Clinic examinations of these patients subsequent to their discharge from the hospital have failed to reveal any neurological abnormalities. The parents of all children state that no personality changes have been noted.

SUMMARY

The administration of chloramphenicol by mouth or by rectum has been demonstrated by other authors to represent a highly effective therapy for meningitis due to *H. influenzae*. The oral or rectal administration of any

therapeutic agent to an acutely ill patient offers several disadvantages. In the treatment of meningitis, the rapid administration of effective therapy is desirable, and it is preferable to overcome the disadvantages of refusal, slow absorption, or vomiting of the medication.

We present six cases of meningitis due to *H. influenzae* which were treated successfully in a manner eliminating these disadvantages by using intravenous chloramphenicol until such time as the clinical condition of the patients justified the administration of oral chloramphenicol.

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SNAPPING THUMB IN INFANTS AND CHILDREN

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SNAPPING thumb in children is unusual and is sparsely reported in the literature. Sixty-six cases have been reported since Hauck's[5] paper in 1922 and in twenty-four of these cases it was present bilaterally. The usual synonyms of this syndrome are trigger thumb and stenosing tendovaginitis of the flexor pollicis longus as described by Hauck from the pathological findings.

TABLE I. CASES REPORTED

AUTHOR	YEAR	NO. CASES
Hauck	1922	2
Kroh	1925	2
Compere	1933	1
Hudson	1934	8
Jahss	1936	10
Beck	1940	20
Zadek	1942	2
Burman	1945	6
Rose	1946	2
Posch and Stofer	1947	1
Sprecher	1949	12

Most of our cases were referred by pediatricians, and it appears that these cases are being encountered initially more frequently by the pediatricians. No reports of the condition could be found in the pediatric literature.

The purpose of this paper is to add seven cases to the literature, three of which are included here, and to report its occurrence in fraternal twins, which may support some congenital predisposition theory. In addition, one of our cases was unusual in that it locked in extension not previously described. A study of all the cases of snapping thumb in infants and children revealed several interesting features peculiar to the disease in children. It was necessary to make the study in this fashion in order that we could arrive at some conclusive information, as there was much divergence of opinion among writers who could observe and report only a small number of cases.

The syndrome is less frequent in children than in adults. While the thumb as well as other fingers may be involved in adults, it appears to be practically always confined to the thumb in children. Only three cases of the deformity in other digits have been reported in children.[1, 6, 13] While the pathology and clinical manifestations appear similar, a striking difference is that there is usually a fixed flexion contracture in children (78 per cent). For this reason, Zadek objects to the term of trigger finger in children because it implies snapping, which he did not observe in his two cases, and hence called the entity stenosing tendovaginitis of the thumb in infants. Snapping is the result of incongruity between the tendon and sheath, the snapping resulting from the passing of the bulbous tendon through the narrowed sheath which occurs both in flexion and extension. The tendon of the long flexor of the thumb is frequently found to have a nodular enlargement associated with tendon sheath constriction at the metacarpal-phalangeal joint which accounts for the incongruous surfaces. On attempted extension of the thumb the tendon sheath either blocks the nodular enlargement on the tendon, preventing extension, or the nodule passes through the tunnel abruptly on forced extension causing snapping. In one of our patients the nodule was dis-

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tal to the constricted sheath which locked the thumb in extension, but in all other reported cases the nodule was proximal to the constricted sheath locking the thumb in flexion. The flexor muscles being stronger are more likely to pull the nodule through the constriction than are the weaker extensors, relatively weak extensor tendons and reduced voluntary control. In cases where the tendon is nodular, bulbous, or enlarged by irregular granulations, the phenomenon of snapping and fixed flexion or extension is easily explained. In some cases there is such a minimal change in the tendon, the locking or

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1.—The flexion deformity held at 140°, as it appeared in a 2½-year-old male.

Fig. 2.—Passive flexion in the same patient as Fig. 1, showing no limitation of this motion.

Fig. 3.—Passive extension in the same patient as Fig. 1, demonstrating marked limitation of this motion with resultant "fixed flexion contracture."

making flexion deformity more prominent. In more advanced cases passive motion is usually necessary to produce flexion and extension. In the final stage even passive motion is insufficient to slide the disportionate tendons through the thickened and contracted sheath. In infants it may be that fixed flexion contracture is more common because of snapping phenomenon is difficult to explain.

Because there is little general information of this entity the diagnosis is infrequently made.[6, 7] The most frequent erroneous diagnoses were "congenital contracture of the thumb" and "dislocation of the interphalangeal joint."

CLINICAL FEATURES

In adults the patients usually present themselves because of a snapping phenomenon which they feel is related to the distal interphalangeal joint rather than the site of the real pathology, the metacarpal-phalangeal joint, while in children the mother states the thumb is in fixed flexion. In only a few instances has the snapping phenomenon been described in children.

curred in flexion, the nodule of the tendon is proximal to the pulley in deeper and more padded tissue at the base of the thumb and cannot be palpated for this reason.

Cases have been reported where a nodule is palpated on the opposite thumb although no symptoms were in evidence.[12, 14] In one case where the asymptomatic nodule was felt in the opposite thumb, symptoms became evident one year later.

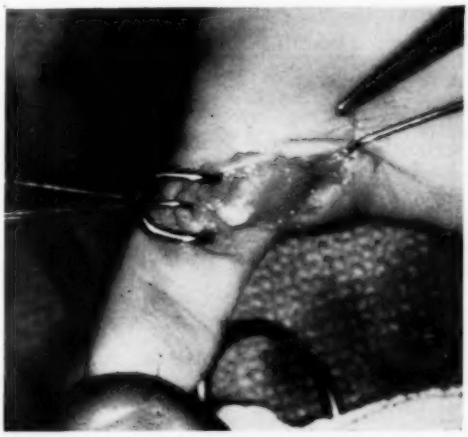

Fig. 4.—The demonstration of the mechanism of locked extension at surgery in a 5-year-old female. The nodule on the tendon can be seen impinged distal to the thickened and constricted tendon sheath, preventing the flexion motion and causing a deformity locked in extension.

A small palpable nontender mass is felt at the metacarpal-phalangeal joint on the flexor surface. This mass is the thickened digital fibrous sheath and the nodular enlargement on the tendon. In only one of our patients was the nodule of the tendon palpable separately from the thickened digital sheath and that was where locking had occurred in extension where the nodule of the tendon was distal to the constricted and thickened sheath and moved with motion of the thumb. In the majority of cases where locking oc-

The age of onset was difficult to determine in infants because it is normal for them to hold their thumbs in the flexed attitude, and the deformity is consequently discovered at a later date. Because of this fact, the onset is described as insidious.

TABLE II. ONSET

No. cases available for study		73
Birth	15	(8 cases gave indefinite history)
First year	4	
Second year	10	
Third year	5	
Fourth year	2	
"Insidious onset"	23	

Distribution according to sex was practically equal with the syndrome occurring in thirty-one males and in forty-two females.

A family history of this syndrome is usually not obtained. The history of trauma was only given as a definite finding in three cases and appears to be incidental.

The deformity occurred bilaterally in 35 per cent of the cases. Twenty-three deformities occurred in the left thumb, twenty-six in the right, and twenty-four were bilateral.

Fig. 5.—The third change was that of actual nodule formation shown at surgery after the incision of the thick sheath.

TABLE III. PHYSICAL FINDINGS

Deformity	Flexion in 72 cases (73% in 120°-145° range)	
	Extension in 1 case	
Motion	No. thumbs available for study	89
	Fixed	67
	Snapping	16
	Not available for study	6
Nodule	Present	47
	Prominent finding in other papers.	

ETIOLOGY

The etiology is thought to be congenital, traumatic, or a combination of both. Infants hold their thumbs normally in a flexed attitude, causing kinking of the tendon over the pulley at the metacarpal-phalangeal joint. This mechanism has been suggested as an etiological agent on a traumatic basis.[12] The theory that trauma is the etiological agent is supported by the demonstration of infiltrating inflammatory cells in the stroma of the tendon or sheath.[10, 12] It is hard to visualize that trauma is the sole etiological agent in infants or children who are not subject to repetition of trauma as in adults. In the adult form it is also more common in females[3, 9] who are not engaged in the same active manual labor as men where the incidence is low. It becomes difficult in both the children and the adult form of snapping thumb to attribute the etiology solely to trauma.

PATHOLOGY

On exposing the tendon sheath it is found to be locally thickened and constricted at the metacarpal-phalangeal joint and in some instances when incised cut like gristle.

The variable findings were in the tendon in which the examiner found

little change in the tendon, which may or may not have warty granulations on the visceral synovium. The second variation was a diffuse bulbous thickening of the tendon, followed by the third form which had an actual nodule formation.

The microscopic findings ranged from no inflammatory reaction in the early cases where trauma had not as yet caused the inflammatory cell response, to inflammatory findings in the cases with longer duration. The amount of connective tissue formation varied with the duration of the deformity and the degree of trauma. The sheath was biopsied in three of our cases and the nodule in one, and none of these cases showed inflammatory change but an increase of collagenous connective tissue. The nodule formation appears to be the result of the duration and amount of trauma. Hudson reported a congenital anomally in a biopsy of a nodule in one of his cases, but this has not been verified by any of the other case reports.

TREATMENT

All authors agree that surgery is the treatment of choice in this syndrome. The operative treatment has been found to be almost uniformly satisfactory, and there were only a few instances of failures.[1, 2, 6] Of ninety thumbs subjected to surgery in the literature, 94.4 per cent, including our seven cases, were corrected following surgery. All conservative measures were failures.[1, 6, 12]

SUMMARY

The literature has been reviewed and seven cases of snapping thumb in children are added to the sixty-six cases previously reported in the world literature. For the first time the syndrome is reported in twins, one of which was bilateral. This may give further evidence for a congenital predisposition theory. In one of our cases locking occurred in extension which has never previously been described previously. Both the thickened tendon sheath and nodule on the tendon were palpable in this case. The chief variance of the clinical manifestations in children is the greater tendency for locking and less frequent incidence in the fingers. Surgery is the treatment of choice with uniformly satisfactory results.

CASE REPORTS

Case 1.—A 3-year-old female, fraternal twin, in whom a flexion deformity of the distal phalanx of the right thumb had been noted for approximately one year. There is no history of snapping. A "nodule" was noticed on the flexor surface of the thumb which blanched on attempted forced extension. Family history: fraternal twin with bilateral "snapping thumb," one other sibling with clubfoot.

Physical examination revealed a flexed distal phalanx of the right thumb at 140°, with motion actively and passively limited in extension at 140°. Flexion motion was complete with no limitation. "Nodule" was palpated at the metacarpal-phalangeal joint. There was moderate pain on attempted extension and blanching of skin over "nodule."

Fourteen months postoperative, there was complete motion present, and no nodule felt. Scar formation was minimal.

Case 2.—A 2½-year-old female noticed inability to extend the left distal phalanx of the left thumb two months before admission. There was no history of trauma. No history of "snapping" was present in this case. Family history was essentially normal.

Physical examination revealed the left thumb in flexed position of ap-

proximately 145° with extension limited at that point actively and passively. A mass was palpated at the base of the thumb which was nontender.

Twelve months postoperative, the patient had normal function, and no palpable nodule. No scar was discernible.

CASE 3.—A 17-month-old male referred by a pediatrician because of bilateral deformity of the distal phalanx of the thumb. There was no history of trauma, and no pain associated with the deformity. Family history was essentially normal, and no congenital deformities.

Physical examination revealed the usual flexion deformity with extension limited at 150°, flexion normal. Enlargement was felt on the flexor surface at the metacarphal-phalangeal joint. Snapping was not present.

Five years postoperative, the patient had normal motion and no palpable nodule. No scar was discernible.

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FUNCTIONAL ASPECTS OF CONGENITAL DEFECTS AFFECTING THE LEFT VENTRICLE

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FUNCTIONAL aspects of congenital defects affecting the right heart, especially disease complexes associated with pulmonary stenosis, have received more consideration than congenital defects affecting the left heart. The right heart syndromes are more amenable to study, especially since the advent of techniques of right heart catheterization and angiocardiography. Catheterization, except for occasional exploration of the left heart through a septal defect, is limited to the right side, and angiocardiography is more informative when visualizing venous shunts into the aorta or left auricle, or in demonstrating right ventricle outflow obstruction. While coaretation of the aorta, which has been studied extensively, may be considered dynamically as primarily affecting the left ventricle, other congenital defects affecting the left heart have received anatomical and pathological rather than functional consideration. Since several of these are fatal during early infancy, opportunity for functional studies have been limited.

Congenital defects affecting the left heart may be considered in three categories, those originating in the left ventricle or myocardium itself, those situated in the region of the aortic valve and manifesting themselves functionally by obstruction to outflow or occasionally by interference with coronary flow, and those situated in the aorta which are also obstructive in nature.

A sequence of patients each representing one of the three categories of abnormality of outflow from the left ventricle offered opportunity for observations of some functional aspects of the left heart syndrome. The three patients showed, respectively, (1) fibroelastosis involving the left ventricle only, in which an angiocardiogram illustrated abnormal outflow dynamics, (2) stenotic obstruction of the area of the aortic valve which resulted in reproducible anginal episodes during exercise, with characteristic ischemic myocardial electrocardiogram patterns, and (3) hypoplasia of the arch of the aorta, associated with a patent ductus arteriosus, producing progressive cardiac failure and pulmonary congestion which was followed by oximetric studies of pulmonary function. The purpose of this paper is to present the clinical aspects of these cases and observations illustrating the functional aspects of each.

CASE REPORTS

Impaired Outflow From Disease of the Left Ventricle

CASE 1.—M. K. No. 517585, a white female, was first admitted to the hospital at 3 months of age, with a history of a common cold for four days, followed by the sudden onset of extreme irritability, rapid grunting

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respirations, and vomiting. Pregnancy and delivery had been uneventful. She had an undiagnosed febrile illness in the newborn period which lasted one week. An x-ray taken at that time showed no abnormality of the heart or lungs (Fig. 1). Physical examination revealed a well-developed, well-nourished infant, ashen in color, and in obvious respiratory distress. The heart was markedly enlarged. No murmurs were heard, and the lungs were clear. The liver edge was palpable 4 cm. below the costal margin. Hemoglobin was 9.8 grams, red blood count 3.8 million, and white blood count 14,600. An x-ray now showed the heart greatly enlarged, globular in configuration (Fig. 2). An electrocardiogram showed a tendency to right axis deviation and S-T_1 was elevated and S-T_3 depressed. The impression was acyanotic congenital heart disease with cardiac decompensation. Following digitalization, oxygen, and chemotherapy she improved remarkably. On the sixth hospital day a faint systolic murmur could be heard, loudest over the pulmonic area, but audible over the whole precordium. An angiocardiogram was done. There was no evidence of intracardiac shunt. The left auricle and left ventricle filled normally, but there was marked delay in the outflow of Diodrast from the left ventricle (Figs. 4, 5, 6, 7). The patient was discharged on a maintenance dose of digitalis, and did well until 6 months of age, although the heart remained large. She was readmitted to the hospital with a second episode of acute respiratory distress. An x-ray (Fig. 3) showed an even larger heart. The electrocardiogram now showed the presence of left ventricular hypertrophy in a heart vertical electrocardiographically. The arterial oxygen saturation was 88 per cent. Biopsy of a muscle showed no evidence of glycogen storage. She again improved considerably, and was discharged home, but at 8 months of

Fig. 1.

Fig. 2.

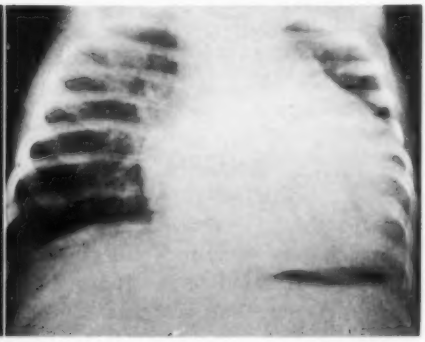

Fig. 3.

Figs. 1, 2, 3.—Posteroanterior views, showing the cardiac silhouette at 6 days, 3 months, and 6 months of age. At 6 days the heart was considered to be normal in size.

age she suddenly developed severe dyspnea. The findings were similar as on the previous admissions, except that the lung fields were now congested. She expired twenty-four hours after admission to the hospital.

At autopsy there was marked fibroelastosis of the left ventricular and left atrial endocardium, with marked myocardial hypertrophy and dilatation. There was marked congestion and edema of the lungs, and mild con-

Fig. 4.

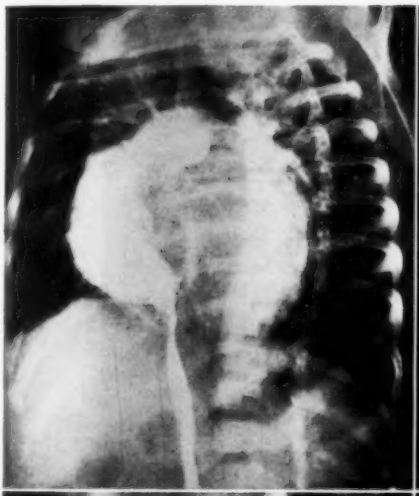

Fig. 5.

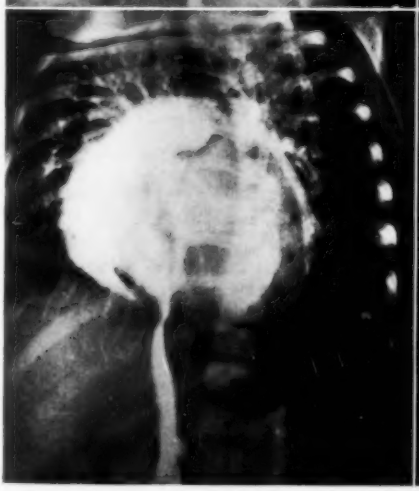

Fig. 6.

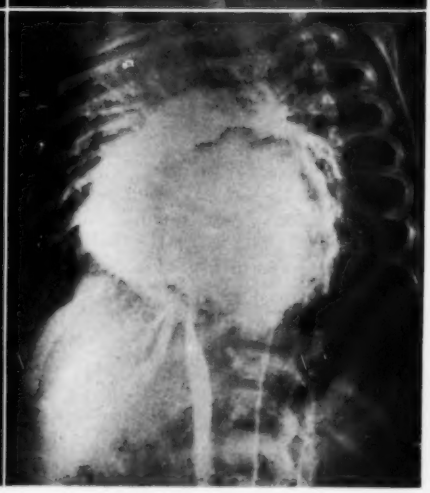

Fig. 7.

Figs. 4, 5, 6, 7.—Angiocardiogram, right posterior oblique views. Injection of Diodrast into right saphenous vein. At ½ second, the right atrium, right ventricle, and pulmonary artery are opacified. At 1½ seconds, the left ventricle begins to opacify and rapidly fills. Even when completely filled at 2½ seconds, there is no Diodrast discernible in the aorta. There has been some retrograde filling of veins from below.

gestion of the abdominal organs. The entire endocardium of the left heart was strikingly opaque, and varied in thickness from 0.5 to 1 cm. (Fig. 8). This was most marked over the endocardium of the interventricular septum in its central portion. The mitral valve leaflets were moderately thickened with small nodules 3 to 4 mm. in size near their free edges. The chordae tendinae were thickened and shortened and the papillary muscles were involved by the endocardial thickening.

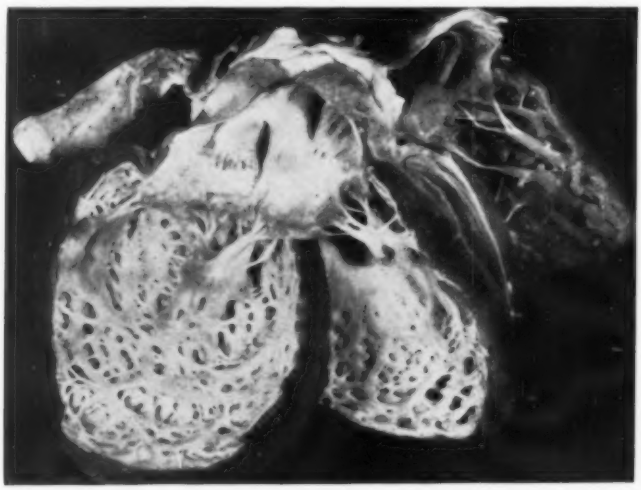

Fig. 8.—There is marked endocardial sclerosis of the left ventricle and left atrium. The endocardium of the right ventricle and atrium, seen posteriorly, is normal.

The aortic valve and the chambers of the right heart were normal. Histologically the endocardial thickening consisted of a mixture of collagen, elastic tissue, reticulum, and ground substance. The myocardium of the left auricle and ventricle showed a rather striking increase in interstitial fibrous tissue, resembling the interstitial fibrosis usually associated with myocardial ischemia. There was also rather prominent dilatation of the venous channels in the lateral portion of the left ventricle.

Impaired Outflow From Obstruction at the Aortic Valve

CASE 2.—D. F. No. 512341, a 5-year-old white boy, was seen in the outpatient department in October, 1950, because of a cardiac murmur first noted at the age of 1½ years. Between 11 months and 3 years of age he had a number of episodes of acute respiratory distress, which were diagnosed as asthmatic attacks. He had frequent colds and sore throats, but these complaints disappeared following tonsillectomy at 3 years of age. Physical examination showed a well-developed, well-nourished boy of small stature, with no evidence of cyanosis or respiratory distress. The blood pressure was 96/70 mm. Hg in the arm and 120/76 in the leg. The heart was not enlarged. There was a loud, coarse systolic murmur of grade 4 intensity maximum at the second right interspace, heard less intensely over the precordium and in the neck. The aortic second sound was audible and equaled the pulmonic second sound in intensity. An x-ray (Fig. 9) showed the heart normal in size and configuration, and the electrocardiogram a tendency to left axis deviation. The diagnosis was aortic or subaortic stenosis and he was followed in the clinic at regular intervals.

The following year he began to have peculiar "fainting spells." These

episodes occurred during or following exercise, particularly running. They began with an ill-defined sensation in the epigastrium and ringing in the ears. He would then become pale, with slightly blue lips, and if physical activity continued, he collapsed. He never lost consciousness completely and there were never any convulsive movements. After an episode he felt tired and frequently went to sleep. He restricted his activities more and more from fear of precipitating an attack. In spite of this restriction of activity the attacks became increasingly frequent and he was admitted to the hospital for further study. An electroencephalogram showed some increased activity, but was interpreted as within normal limits. A ballistocardiogram was normal (Fig. 10). An exercise tolerance test was done. After walking on an electrically driven treadmill for 84 seconds at a speed of four miles an hour, with a grade of 3 per cent, he suddenly developed severe substernal pain, became pale, and perspired profusely. The onset of pain occurred at a pulse rate of 190 a minute, measured by a recording tachometer. An electrocardiogram immediately before and after exercise showed striking differences (Fig. 11). There was a coronary pattern in the postexercise tracing, with marked S-T depression. After one minute both

Fig. 9.—Posteroanterior view. The heart is normal in size and silhouette.

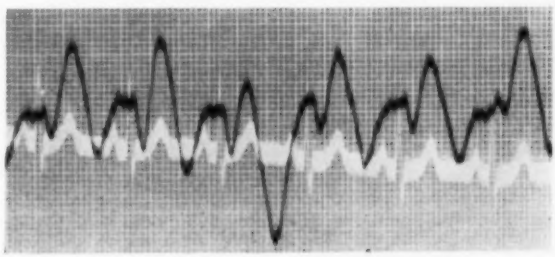

Fig. 10.—Ballistocardiogram. Maximum systolic force (F), 25.0 grams; pulse 96; Maximum minute force, 2.4 kg. per minute. The configuration of the HIJK complexes is normal. The various intervals (Q-I, I-J, Q-K) are shorter than in adults. The prolongation of Q-J sometimes seen in adults with aortic stenosis is absent. (Tracing and interpretation courtesy Dr. R. J. Jones, Department of Cardiology.)

the pulse and the electrocardiogram returned approximately to their resting values. The blood pressure was 106/64 before exercise and forty seconds after exercise terminated 90/48. next few days this was observed during crying. On the sixth day there was a temperature elevation to 38.2°. The heart rate was 120 a minute, the heart sounds were abnormally loud, but no

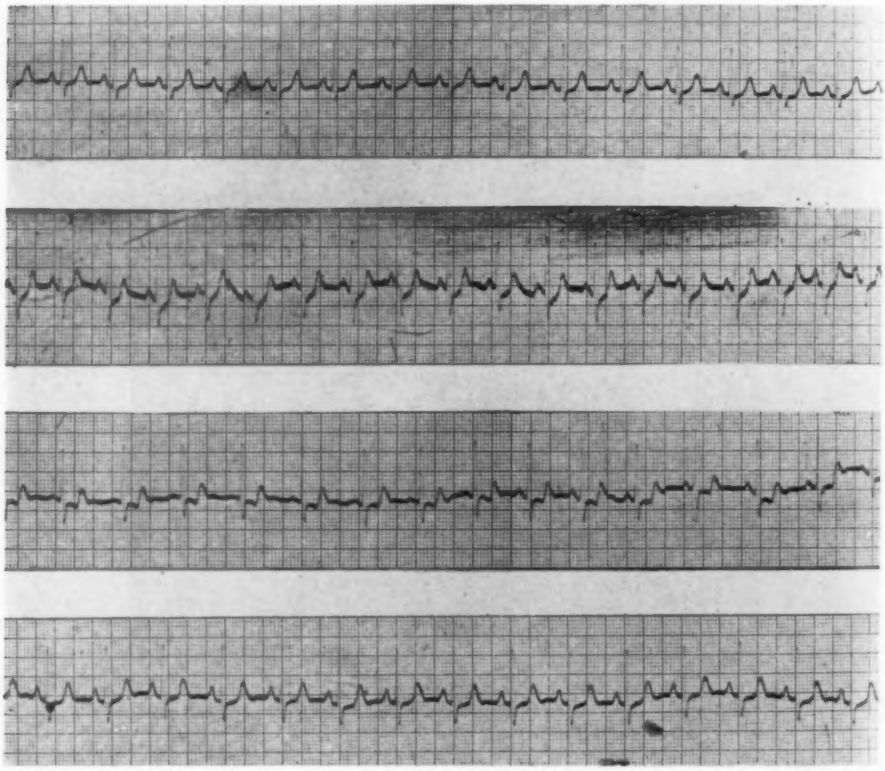

Fig. 11.—Electrocardiogram, Lead II. Row 1, resting. Row 2, 6 seconds after exercise on the treadmill, severe substernal pain still present. Row 3, 30 seconds after cessation of exercise. Pain is disappearing. Row 4, 60 seconds after exercise. Pain has disappeared, and the S-T segment has returned to normal.

Impaired Outflow From Aortic Obstruction

CASE 3.—B. L. No. 522505 was a white female infant, full term, birth weight 3,230 grams. The mother probably had rubella at 5 weeks' gestation. Delivery was normal and physical examination at birth and on admission to the nursery showed no abnormalities. On the third day slight cyanosis appeared while feeding, and for the murmurs were heard. Brachial and femoral pulses were easily palpable, but accurate blood pressure determination could not be obtained. Respiration was rapid and shallow, but there was no obvious respiratory distress. A few transient wheezing râles were heard in both lungs, and an x-ray (Fig. 12) showed a few mottled areas of increased density in the right lung field. The cardiac silhouette was considerably enlarged. An electrocardio-

gram showed some evidence of left ventricular hypertrophy. The arterial oxygen saturation by the oximeter method was 93 per cent while sleeping, but decreased to 75 per cent when crying. The infant was placed in an environment of high oxygen and high humidity and given antibiotics for questionable pulmonary infection, although congenital cardiac or pulmonary abnormality seemed probable. On the seventh day a progressive de-

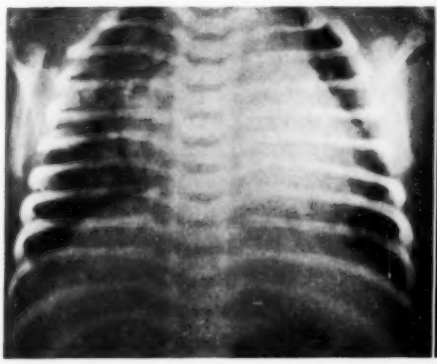

Fig. 12.

Fig. 13.

Fig. 12.—Posteroanterior view, sixth day of life. The heart is moderately enlarged, although some rotation accentuates this. There is some infiltration in the lung fields.

Fig. 13.—Posteroanterior view, sixteenth day of life. The heart is grossly enlarged, and there is marked infiltration in the lungs.

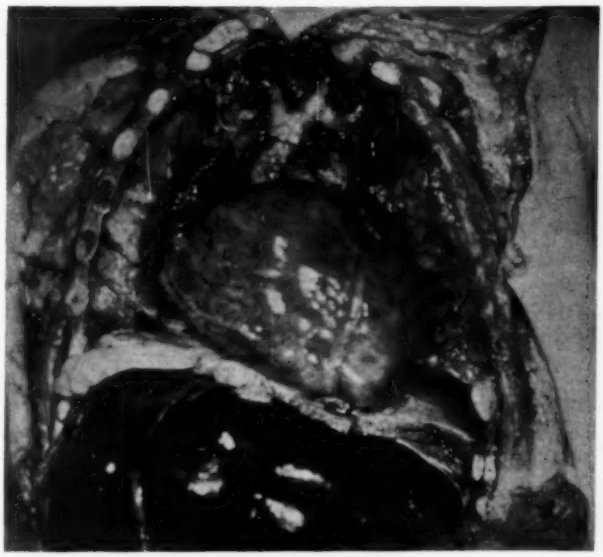

Fig. 14.—The heart and great vessels at post mortem. The narrowed aortic arch is remarkably constricted just below the origin of the left subclavian artery. The large patent ductus arteriosus is not well seen.

terioration in her condition began. There was acute respiratory distress out of oxygen, with frank cyanosis. The cyanosis was most marked over the upper part of the trunk and the head. The heart rate was 180 a minute, but the heart sounds remained remarkably loud. Moist fine râles were heard throughout both lungs. The liver edge was palpable 2.5 cm. below the right costal margin and gradually increased to 6 cm. As the cyanosis became more pronounced, edema developed over the face, neck, and vulva. A faint variable systolic murmur appeared along the left sternal border. On the sixteenth day, an x-ray (Fig. 13) showed marked cardiac enlargement, with areas of patchy densities in both lung fields. The electrocardiogram now showed a right axis deviation. Oximetric studies are shown in Table I. Death occurred on the thirty-sixth day.

Table I. Arterial Oxygen Saturation, Case 3, Ear Oximeter Method

		Breathing air	Breathing oxygen
6th day	Sleeping	93%	
	Crying	75%	
17th day	Air hunger, cyanosis	62%	90%
26th day	Air hunger, cyanosis	53%	90-93%
32nd day	Air hunger, cyanosis	63%	92-94%

At autopsy the pertinent findings were confined to the heart and lungs. The pericardial sac contained 5 to 10 c.c. of clear fluid. The heart was moderately enlarged and weighed 65.2 grams, and showed both hypertrophy and dilatation. The ascending aorta was normal in caliber to the origin of the innominate artery, but the arch was diffusely narrowed, approximately to the size of the innominate artery (Fig. 14). Distal to the origin of the left subclavian artery the aorta became smaller and the diameter just above the insertion of the ductus arteriosus was less than 2 mm. The ductus arteriosus was large, 1.2 cm. in diameter, and patent, and continuous with the descending aorta. The wall of the left ventricle was 1 cm. in thickness and the right 0.5 to 1 cm. A small low interventricular septal defect was present, 5 mm. in diameter. The lungs were collapsed and congested except for patchy aerated areas anteriorly.

Discussion

While the type of congenital anatomical defect present differs in each patient, from the functional aspect they have in common varying degrees of obstruction to outflow from the left ventricle and may be considered together as representing a functional type of left heart syndrome. In newborn infants and in infants during the first year of life who decompensate without being cyanotic differential diagnosis is arrived at with difficulty. Under these circumstances these types of defect, together with failure related to an anomalous coronary artery, or to glycogen storage diseases, include the great majority of such patients.

Fibroelastosis most frequently involves the left ventricle with or without involvement of the mitral and aortic valves, although it may occur in the right ventricle and in one or both auricles. Several explanations of heart failure in the presence of this disease have been suggested. Weinberg and Himelfarb[1] suggest that the endocardial thickening which is characteristic of this disease interferes with coronary blood flow by obstructing arterioluminal, arteriosinusoidal, and Thebesian vessels. Edmonds and Seelye[2] accept this explanation. Prior

and Wyatt[3] were impressed with the degenerative changes in the papillary muscles and suggested interference with their function as another factor contributing to failure. The same authors also suggest a mechanical explanation for failure, that the thick rigid endocardium may limit both diastolic filling and systolic expulsion of blood. There is some evidence in the present case to support each of these theories.

The case presented is especially interesting in that there was no obvious cardiac enlargement on the sixth day of life. This can be explained only as a reflection of the diminished circulatory load on the left ventricle during fetal life, or indicative of progression of the disease during infancy.

The angiocardiogram demonstrates the gross functional effect of the pathology. There is no limitation of diastolic filling of the left ventricle but delay and difficulty in systolic expulsion is well visualized. Even after the left ventricle was completely opacified no Diodrast appeared in the aorta. Unfortunately the angiocardiogram was terminated at this point and the total delay could not be adequately timed, although the outflow was greatly prolonged. It is suggested that dilation of the ventricular cavity results in consequence of difficulty in systolic expulsion, whatever the correct explanation of this might be, and a resulting increase in residual volume. The ultimate result is failure.

There is no adequate way, in Case 2, of differentiating between valvular aortic stenosis and subaortic stenosis. While the aortic second sound was present, this was reduced in intensity, suggesting involvement of the aortic valve. However, with reduction of blood flow by obstruction in the subaortic area, a reduced second sound may also be present, and the presence or absence of a second sound of normal intensity is not helpful in diagnosis.[4] It is generally stated that congenital obstruction in the aortic area is more frequently subaortic stenosis than aortic valvular stenosis, but Potter[5] reports that in nearly 10,000 autopsies in the fetus and newborn infant she has never encountered subaortic stenosis while aortic valvular stenosis has been observed relatively frequently. While the blood pressure may be considered normal and there is no abnormality of cardiac contour, no cardiac enlargement, and no poststenotic dilation of the ascending aorta, there is ample evidence that these findings are not necessary for the diagnosis of aortic stenosis.[6] The ballistocardiogram, which is essentially normal, gives no evidence of dynamic obstruction to aortic outflow in the resting state. The diagnosis rests upon the location and auscultatory characteristics of the murmur.

Angina pectoris or syncope has been reported with relative frequency in acquired aortic stenosis in adults,[7, 8] but the diagnosis of angina pectoris has not been supported by appropriate electrocardiogram findings in congenital aortic stenosis. The electrocardiogram during recovery from exercise-induced angina (Fig. 10) shows changes in the S-T segment grossly abnormal[9, 10] and greater than the changes which occur normally during comparable exercise.

This tracing resembles one obtained by Marvin and Sullivan[8] after exercise-induced angina and syncope except that no arrythmia occurred.

The mechanism of origin of angina or syncope in patients with aortic stenosis has been the subject of considerable speculation. Marvin and Sullivan believe that the evidence is not sufficient to accept the attractive idea that fainting is due to cerebral anemia resulting from deficient outflow into the aorta in the presence of stenosis of the aortic orifice. They suggest a carotid sinus reflex as the precipitating mechanism. However, Contratto and Levine[7] did not find the carotid sinus hyperirritable in the 22.7 per cent of their series who had angina. Whatever the precipitating mechanism, Grishman, Steinberg, and Sussman[11] and other authors call attention to the frequency of precordial or epigastric pain on exertion, and to dyspnea and syncopal attacks. Of the twenty-three patients followed by these authors, three were dead at 4, 9, and 48 years of age. It seems clear that even in the congenital types of obstruction at the aortic area syncope and angina of effort may occur.

Case 3 represents obstruction within the aorta itself. The post-mortem findings were similar to those commonly found in infantile coaretation. Judging from the clinical and laboratory findings, the main difficulties of this patient were related to obstruction to outflow from the left ventricle, increasing the load of the left ventricle sufficiently to initiate early failure. The spectacular forceful precordial impulse, the loud heart sounds and the tendency to left ventricular hypertrophy in the electrocardiogram on the sixth day of life are interpreted as a reflection of obstruction to left ventricular outflow. Blood flow to the lower extremities was satisfactory as indicated by good femoral pulses. Although blood flow to the descending aorta is usually attributed to flow from the pulmonary artery through the ductus arteriosus in this situation, the experimental studies of Gupta[12] and the clinical study of Johnson, Ferencz, Wiglesworth, and McRae[13] do not support this thesis. Cyanosis was more marked in the face and head, and with the infant breathing oxygen there was never any detectable difference in color between hands and feet. Because of the infant's precarious condition direct blood pressure recording and comparison of the saturation of brachial and femoral artery blood were not done. On the seventh day of life congestive failure developed, which at first was mainly left ventricular failure with the signs and symptoms of acute pulmonary edema. The signs of right ventricular failure gradually became more marked, manifested by peripheral edema, curiously confined to the head, neck, and vulva, and increasing enlargement of the liver. The oximetric readings indicated the pulmonary origin of the cyanosis. Arterial oxygen saturation with the infant in ambient air became very low, 52 to 60 per cent, when pulmonary edema developed. In oxygen these values rose to 93 per cent when the high alveolar oxygen pressure overcame diffusion difficulties related to pulmonary edema. The first observation indicated a drop in saturation during crying on the sixth day, an infrequent finding at this age[14] and presumably related to mild pulmonary congestion. The low arterial saturation while breathing air and the nearly normal saturation while breathing oxygen was a consistent pattern throughout the period of decompensation.

The consequence of obstruction to outflow from the left ventricle is manifested by a variety of symptoms and different diagnostic techniques are required to identify the functional difficulties which this general syndrome produces. The cases presented represent impediment to blood flow at different anatomical levels in the course of blood flow from the left ventricle. Difficulty in outflow resulting from disease of the ventricle itself was best demonstrated by angiocardiography, while obstruction to outflow in the area of the aortic valve manifested itself functionally by angina, the myocardial ischemia being identified only by the electrocardiogram after exercise, the resting tracing being normal. Obstruction to flow in the aorta resulting from aortic hypoplasia manifested itself by progressive pulmonary congestion, the functional aspects of which were followed by serial determinations of arterial oxygen saturation by the oximeter.

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CHOLEDOCHAL CYST

Report of a Case With Unusual Features

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CHOLEDOCHAL cyst, or cystic dilatation of the common bile duct, is an unusual condition, for less than 200 cases have been reported in the medical literature. The importance of this disease arises from the fact that it has a clinical picture that is easily recognized and amenable to surgical therapy. A high mortality has often occurred because of delayed diagnosis and improper treatment. The case reported here did not present the clinical findings for an accurate preoperative diagnosis, and was in an age group where the condition is not ordinarily considered. Prompt recognition at the operating table, however, resulted in a good recovery.

CASE REPORT

The patient, J. S., was a white female admitted on Aug. 1, 1951, at 2 months of age for jaundice since 3 days of age, with persistent, light-colored stools and dark urine. Past and family history were negative. The child was one month premature, but birth was normal in all other respects. Weight at birth was 5 pounds 9 ounces. The child had appeared normal other than for the presence of jaundice, and weighed 9 pounds at the time of admission.

Physical examination showed a healthy female infant with moderate jaundice. The liver was palpable 3 to 4 cm. below the costal margin. No other mass could be felt. Blood tests showed red blood cells, 3.5 million, hemoglobin 10.5 Gm., and white blood cells, 8,500, with a normal differential cell count. Urinalysis revealed normal findings. The Kahn serologic test was negative. All stools appeared acholic over twenty days of observation, and chemical tests for biliary pigments were reported negative on three occasions. The urine contained bile; urobilinogen was reported present on four occasions. The icteric index was 7.3 units on August 2; serum bilirubin 2.5 mg. direct, and 5.1 mg. indirect on August 7; icteric index, 16.5 units on August 14. Cephalin cholesterol flocculation was negative at forty-eight hours; prothrombin time was 100 per cent. Red cell fragility was normal; the Rh factor was positive. Duodenal contents obtained by aspiration were negative for bile; lavage with magnesium sulfate produced no change. The presence of urinary urobilinogen on four occasions led to repeated inspection and chemical testing of the stools, which always failed to show biliary pigments. The urobilinogen may have resulted from absorption from the cyst and common bile duct. X-rays of chest and abdomen showed normal findings.

The general condition of the child was good. Biliary atresia appeared to be the most likely diagnostic possibility, although the low level of the serum bilirubin was unusual. Choledochal cyst was discussed as rarely occurring in infants. A laparotomy was

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The opinions expressed are those of the authors, and do not necessarily reflect the views of the Medical Department of the Navy or of the Navy Department.

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performed by one of us (E. H. D.) on August 21 through a right upper rectus incision. A 5 cm., thin-walled cyst was promptly found deep in the right upper quadrant and contained bile on aspiration. The gall bladder was at the superior pole of the cyst and appeared normal, being about 1 cm. in diameter. The liver appeared normal. The cyst had the typical paraduodenal location of a choledochal cyst of the common bile duct. No dissection of the cyst was done. A two-layer, side-to-side anastomosis of the cyst to the duodenum was performed with an outer layer of interrupted sutures of arterial silk and an inner layer of continuous 00 chromic catgut, producing a 2 cm. anastomotic stoma. A drain was placed to the subhepatic space and the wound closed in layers with retention sutures. Oral feedings were begun the second postoperative day, and biliary pigments were noted in the stool on the fourth. The jaundice faded promptly, and was absent on the tenth postoperative day. The drain and the retention sutures were removed on the ninth postoperative day. A transient febrile episode on the nineteenth postoperative day resulted from an otitis media which responded promptly to penicillin therapy.

The patient was discharged on the twenty-first postoperative day and when last seen six months later weighed 19 pounds. A photograph taken on March 31, 1952, is shown in Fig. 1. There have been no episodes suggestive of cholangitis.

Fig. 1.—Photograph of J. S. taken on March 31, 1952.

CLINICAL FEATURES AND REVIEW OF THE LITERATURE

The literature has been reviewed in detail by Zinninger and Cash (1932),[1] Gross (1933),[2] Poate (1941),[3] and Shallow and associates (1943, 1946).[4, 5] About one-fourth of the cases reported have come from Japan. Recent individual case reports have been made by Sullivan and Dmytryk,[6] Davis,[7] McLaughlin,[8] Kelsey,[9] Fleming,[10] Blegen and Boyer,[11] Irwin and Morison,[12]

Hutchins and Mansdorfer,[13] Berkley,[14] and Blocker and co-workers.[15]

There is a marked sex factor in the incidence of this disease, about 75 per cent of the cases occurring in females. Symptoms are usually present before the twenty-fifth year of life, although a few cases have been seen in persons over 60 years of age. Chesterman[16] has recorded twelve cases with onset or severe exacerbation of symptoms during pregnancy or the puerperal period. The etiology is uncertain, but is apparently a combination of an anomaly occurring in the embryo during the process of recanalization of the biliary cords, and recurrent, partial to complete, biliary obstruction at the junction of the lower end of the cyst with the common duct. The cause of the recurrent obstruction has been variously suggested to be inflammatory stenosis, valve formation, and kinking.

The size of the cyst varies from 30 c.c. to 5,000 c.c. The wall is a few millimeters in thickness, and is composed mainly of fibrous tissue. An epithelial lining is rarely present. The contents are bile with the varying changes seen with stasis, infection, or obstruction. Gallstones have been found in four instances.[17] The lower portion of the common duct is usually small, and in some instances is completely obliterated; rarely does the dilatation extend low enough to involve the entrance of the pancreatic duct. Some cases have no demonstrable obstruction to the common duct distally; but in such instances obstruction may arise from kinking of the junction of the cyst and common duct. The cystic and common hepatic ducts usually enter the cyst separately; rarely does the cyst extend high enough to involve the right and left hepatic ducts. The gall bladder is usually small and apparently nonfunctional. The common hepatic duct is moderately dilated and hypertrophied; a mild degree of cirrhosis is often present in the liver.

Clinical symptoms usually appear in the first few years of life, but less than 5 per cent have symptoms before 6 months of age.[18] The reviews of Zinninger and Cash,[1] Gross,[2] and Poate[3] each contain one case in an infant 1 to 2 months of age. The patient reported by Gilliland and associates[19] was operated upon at 4 months of age, and the cyst contained 850 c.c. of bile. Stools had been clay colored from birth, and jaundice was present from the fifteenth day of life. The patient reported by Keating and Murphy[20] was operated upon at 2½ months of age after having been jaundiced from birth; no communication could be found between the cyst and the duodenum at autopsy. The case of Ripstein and Miller[21] was the first reported example of concurrent biliary atresia and choledochal cyst. The occurrence of cysts in infants emphasizes the congenital aspect of the etiology, but the infrequency with which such cysts are found suggests that recurrent obstruction contributes to the development of the larger cysts.

The triad of tumor, jaundice, and abdominal pain has received due emphasis in the literature, and the diagnosis can be made easily when this combination of findings is considered. A mass has been palpated in about 70 per cent of the cases. The size and firmness of the mass have been noted to increase during acute painful episodes. Jaundice has been noted in 70 to 80 per cent of the cases and is associated with acholic stools in the presence of complete biliary obstruction. Abdominal pain occurred in 60 to 70 per cent of the cases, and varied from a vague ache to acute colic of the right upper quadrant, resembling that seen with biliary calculi. Fever and vomiting have been less constantly noted. All symptoms are intermittent: young adults often give a history of recurrent abdominal discomfort since early childhood.

X-ray studies may be of some benefit. Calcification is rarely seen on plain abdominal films. Duodenal displacement may be present in larger cysts. The most significant test in the ab-

sence of jaundice is the cholecystogram, which usually fails to outline the gall bladder.

Diagnostic errors usually arise simply from a failure to consider the possibility of a cyst. In the absence of a mass, some form of recurrent hepatitis is usually diagnosed, and considerable liver damage may occur before surgical exploration is done. Often the condition is not recognized at operation until extensive dissection has resulted in injury to the hepatic ducts, although the presence of a cyst containing bile in conjunction with a normal gall bladder is practically diagnostic.

No case of spontaneous cure of the cyst has been reported. External drainage of the cyst has a high mortality, probably because biliary decompression prevents bile from being forced through the narrowed distal common duct. Resection of part of the cyst has also carried a high mortality, although a few successful cases have been reported. Side-to-side anastomosis of the cyst to the duodenum is the simplest technical operation and has the lowest operative mortality. This procedure was first done successfully by Bakes in 1906 and has continued to give good results. Some authors have suggested resection of the greater portion of the cyst in order to minimize regurgitation of intestinal contents. This procedure is of doubtful value because of the high mortality rate. The cyst shrinks markedly after decompression, and cholangitis has not been a marked postoperative complication of patients with a side-to-side anastomosis. A Roux-Y type of anastomosis of the cyst to a defunctionalized loop of jejunum has been accomplished in two instances[14, 17] in order to minimize regurgitation of intestinal contents.

The ultimate prognosis in these patients is chiefly unknown, for few long-term follow-up reports exist in the literature. Symptoms suggestive of mild, recurrent cholangitis have occurred in a few instances. Eleven four- to five-year follow-up reports have been found in the literature by Shallow and associates. In 1941 Gross had followed five patients, 6 to 19 years of age, one of whom had recurrent cholangitis. The unusual case of Swartley[22] with double hepatic ducts, one of which contained a cyst, died with portal hypertension several years after ligation of the hepatic duct.

DISCUSSION

Differentiation of choledochal cyst from biliary atresia is seldom necessary, because choledochal cysts are rarely symptomatic in the first few days of life. However, the case reported here emphasizes the fact that choledochal cyst must be considered in the differential diagnosis of jaundice in all age groups, especially when the jaundice is recurrent or associated with a mass. It is possible in the case reported here that the common bile duct distal to the cyst is completely occluded, thus giving rise to the early and persistent jaundice. Exploration of the common duct at operation was not done because of the high mortality associated with extensive dissection in these patients. Persistent light-colored stools from birth indicate a complete biliary obstruction, although the low level of the serum bilirubin and the healthy appearance of the liver at operation are more in keeping with an incomplete obstruction.

The appearance of this condition at an early age emphasizes the probable embryological origin of the disease as a localized cystic dilatation of the duct. The clinical variations seen apparently arise from the degree of biliary obstruction which develops, depending on whether it is mild and recurrent or marked and persistent. It is noteworthy that no instances of asymptomatic cysts have been reported as incidental autopsy findings, although some patients have been seen whose only complaint was the presence of a palpable tumor. The recurrent biliary obstruction associated with the

development of a cyst apparently produces enough symptoms to make clinical recognition possible during the life of the patient.

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CARDIO-CHALASIA IN INFANCY

With a Review of the Literature, Report of a Case, and a Suggested Method of Treatment

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IT IS considered that references to the condition of cardio-chalasia or cardio-esophageal relaxation in infancy, especially in this country, are sufficiently rare to merit publication of a single case.

REVIEW OF THE LITERATURE

Robins and Jankelson,[1] whose practice was confined mainly to adults, coined the term cardio-esophageal relaxation. They described the condition in 103 patients, all of whom had symptoms sufficiently distressing to cause them to seek medical opinion. They found the lowest one to three inches of the esophagus to be dilated, either tubular or globular in appearance, depending on the degree of reflux. It was considered that it was a common but unrecognized condition and they presented two theories as to the etiology:

(a) Increased intragastric pressure, due to hyperperistalsis or hypertonicity, on a liquid medium in the stomach, producing equal pressure on both openings of the organ, the weaker or cardiac sphincter giving way.

(b) Disturbance in the balance of the autonomic nervous system. They found that, with physiological doses of physostigmine salicylate, the cardio-esophageal relaxation showed a tendency to diminish. Atropine increased the degree of reflux.

Friedenwald and associates[2] reported finding a patulous cardia in ten of the thirteen patients with peptic ulceration of the esophagus examined.

Wyllie and Field[3] described six children with a history of intermittent vomiting and hematemesis from birth. One was thought to have a congenital short esophagus, another was described as having stricture of the esophagus, while in the remaining four, laxity of the cardia with resultant hemorrhagic esophagitis was suggested as a cause for the symptoms. In all cases, with the exception of the one described as an esophageal stricture, cardio-esophageal reflux was demonstrated radiologically.

Allison[4] mentions seven esophageal ulcers found in children between 6 months and 5 years of age, but in these, symptoms were first noticed after weaning, mainly vomiting following solid food. In his opinion, the commonest cause of ulceration of the esophagus is a sliding hiatal hernia with esophageal shortening. He stated that the diaphragmatic defect may be present at birth, so that an infantile hernia can lead to fibrosis and subsequent fixation of the esophagus in the first weeks or months of life. Many of these types are called congenital short esophagus.

In a review of nine cases of congenital short esophagus with a thoracic stomach, Findlay and Kelly[5] reported that in seven there was a history of vomiting from birth. In several, the widening of the esophagus below the level of the stenosis was so marked that it was thought to be due to insufficiency of the cardia.

Neuhauser and Berenberg in 1947,[6] regarded persistent relaxation of the hiatus esophagus as an important but rather infrequent cause of vomiting in the newborn infant. They found twelve patients with this condition in three years. Later (1950), the same authors reported twenty-four cases in five years.

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Allen[7] described the condition in three infants and noted the lack of the usual amount of intestinal gas in one case and said that atropine produced contraction of the cardia in one of his infants.

Caffey[8] states that regurgitation of a barium mixture from the stomach into the lower esophageal segment is a common finding in infants and young children. Neuhauser and Berenberg[6] (1950), however, in 2,000 barium meal examinations on newborn infants with vomiting, found only twelve who showed any degree of relaxation of the cardia.

MECHANISM OF THE CARDIA

There is considerable controversy as to the presence and location of a cardiac sphincter. Jackson[9] considered that the diaphragmatic pinchcock action was the only one of importance, but Harrington[10] found that during 500 operations, he could, in 35 per cent, insert one or more fingers between the esophagus and the margins of the diaphragmatic opening. Lendrum[11] examined 150 cardias histologically and found no localized muscle thickening.

Alvarez[12] states that there can be no question about the fact that there is a narrowing of the lumen at the point where the esophagus joins the stomach with enough of a sphincter muscle to delay the passage of material from the esophagus into the stomach and to interfere with regurgitation of gastric contents. He also believes there is a "diaphragmatic cardia" which is mainly brought into play when the intra-abdominal pressure is greatly raised as in lifting or straining at stool. That the diaphragmatic sphincter is not of great importance is indicated by the fact that persons who have a diaphragmatic hernia or who have had a phrenicotomy do not seem to complain of regurgitation. From a study of comparative anatomy, he thinks that weakness of the cardia may be an inheritance from some birds and mammals, in some of which disgorging of food is physiological. The bat, on the other hand, must have a very powerful cardia. Alvarez quotes Hurst as describing a "functional" sphincter at the cardia about 1 inch in length and situated below the diaphragm.

Wyllie and Field[3] quote the fact that Knight, after excising the sympathetic fibers surrounding the celiac axis and left gastric arteries in cats, produced a patulous cardia with resultant regurgitation.

Allison[4] describes the valvelike mechanism produced by the angle between the esophagus and the fundus of the stomach. The elastic recoil of the oblique muscle fibers of the stomach is said to increase its effectiveness. He also describes two other factors—the thick wedge of muscle fibers of the diaphragmatic pinchcock filling the angle and the enclosure of the lower end of the esophagus in a thick-walled tunnel of the diaphragmatic crura contracting during inspiration.

CASE REPORT

G. J. R., a male infant, the first child of healthy parents, was born at full term following a normal pregnancy and delivery on June 25, 1951, weighing 6 pounds 5 ounces. He was first seen when 18 days old, with a history of repeated vomiting within a few minutes of completing his feedings. The vomit had not been projectile and was reported as being bile-stained on occasions. He was breast fed but complementary feedings of National dried milk were being given. His mother stated that he was a contented infant who took his feedings normally. His bowels were said to be constipated.

No abnormal physical signs were detected on routine physical examination but he was found to weigh only 6 pounds 5 ounces. On several occasions during feeding, it was found impossible to palpate a pyloric tumor and true peristalsis was not seen.

On July 17, a plain radiograph was reported as showing very little gas in

the jejunum, possibly as a result of hold-up at the pylorus. Accordingly, on July 25, a barium meal examination was carried out, but no evidence of a delay at the pylorus or elsewhere in the alimentary tract could be found. During this period, his weight had only increased very slightly and the vomiting continued in spite of adjustments in the feeding routine, etc.

He was admitted to the ward on August 26.

Again, no abnormal physical signs were elicited apart from wasting. There was no evidence of dehydration. All investigations, including blood count, urine and cerebrospinal fluid examinations, blood biochemistry, and chromatography of the urine, were found to be within normal limits.

Various attempts to control the vomiting, including esophageal feeding and giving feedings thickened with cereals, produced only a very temporary improvement.

On two occasions, he was noted to have a typical "coffee-ground" vomit. The presence of blood was confirmed by laboratory tests.

At this time, he seemed to give an impression of ruminating and thus, on September 25, a further barium meal examination was carried out. This time, when the barium mixture had entered the stomach, the table was inverted into the Trendelenburg position (approximately 30 degrees from the horizontal) and, without any external pressure on the abdomen, there was an immediate reflux into the esophagus. A persistent "niche" shown in the radiograph (Fig. 1) was found at the lower end of the esophagus. It was considered possible that it was caused by the presence of a small ulcer crater.

He was then propped up for an hour after feedings which were given every two hours with added alkalies. He did not show any real improvement until he was nursed in the "chair" designed by Sister D. N. Roberts (Fig. 2). This marked the beginning of improvement, which has been steady and interrupted only by a temporary acute respiratory infection. His vomiting ceased within a few days and has not recurred. His weight chart has shown a steady rise (Fig. 3). The diet now includes cereals, homogenized soups, etc.

A further barium meal examination on December 10 still showed considerable reflux but after careful study no evidence of gastric herniation, ulceration, or stenosis of the esophagus could be found.

Fig. 1.

DISCUSSION

As stated by Neuhauser and Berenberg,[6] Allen,[7] and others quoted above, it is felt that cardio-chalasia may not be as rare in infancy as the scarcity of reports in the literature suggests. The diagnosis should be considered in any infant presenting with a history of vomiting from birth or soon afterward. Hematemesis is probably a relatively common occurrence, as re-

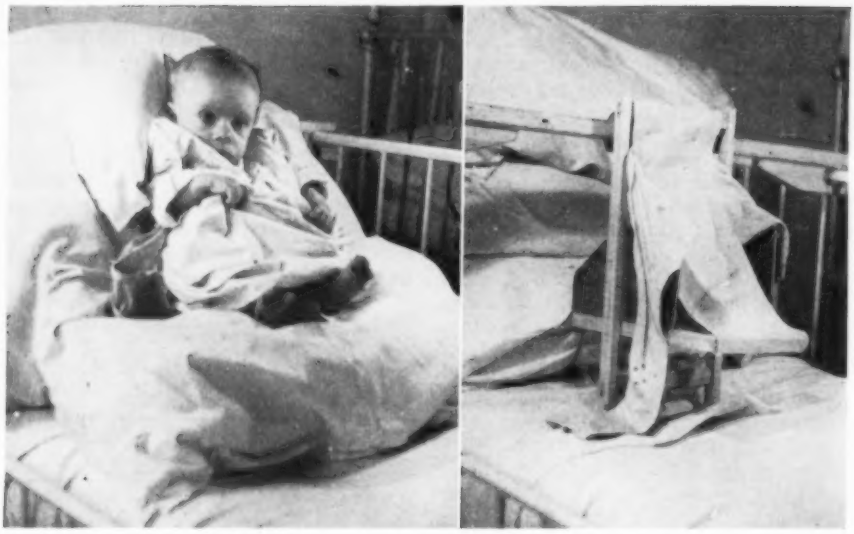

Fig. 2.

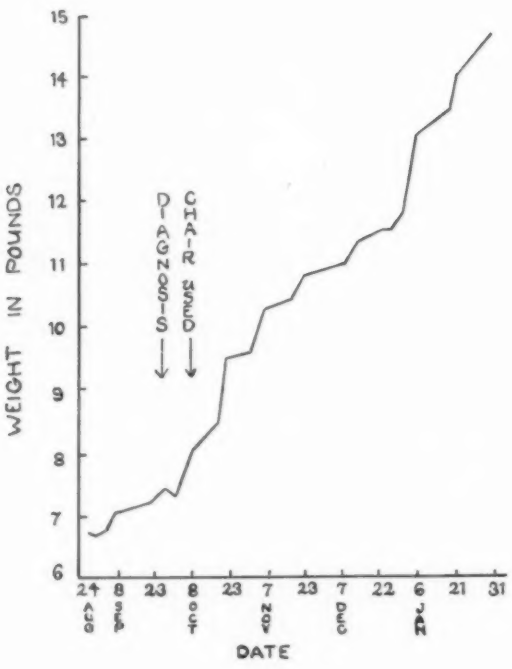
WEIGHT IN POUNDS
15
14
13
12
11
10
9
8
7
6
DIAGNOSIS
CHAIR USED
24 AUG
8 SEP
23
8 OCT
23
7 NOV
23
7 DEC
22
6 JAN
21
31
DATE

Fig. 3.

ported in Wyllie and Field's[3] series. Another point of interest quoted by these authors was the occurrence of a sharp cry immediately prior to the act of vomiting. It is felt also that this condition should be considered in infants previously called "ruminators" or "feeding problems."

As mentioned by previous authors, confirmation of the presence of cardio-esophageal reflux can only be obtained by x-ray screening in the Trendelenburg position following ingestion of a barium meal. Esophagoscopy would probably yield useful information but would not be justifiable in such a case in a young infant.

There does not seem to be much doubt that the condition of the cardia is such that acid gastric juice is allowed easy access to the lower esophageal segment and could lead to esophagitis or even peptic ulceration of the esophagus. Allison[4] believes that in all these cases ulceration and stenosis of the esophagus occurs early and that the process is rapid. Because of this, he recommends early operation. However, the patients in his series of cases ranged from 6 months to 5 years in age and, in all, vomiting started with weaning. It is considered that three rather similar conditions probably exist:

(a) Allison's type: Infantile hiatal hernia with esophageal ulceration and stenosis.

(b) Pure cardio-chalasia with onset of vomiting from birth and possibly esophagitis in untreated cases.

(c) The rare congenital short esophagus with thoracic stomach. Probably many cases previously diagnosed as such belong in actual fact to Allison's group.

It is agreed that in this latter type early operation is essential while the esophagus is sufficiently elastic to be brought below the diaphragm. However, it is submitted that, as found by Wyllie and Field,[3] Neuhauser and Berenberg,[6] Spohn and Campbell,[13] and Allen,[7] in cases of pure cardio-chalasia, treatment should be conservative—frequent, thickened feedings with added alkalies if there is any evidence of esophagitis or ulceration, and the maintenance of an upright posture for periods after feedings, or, preferably, throughout the whole twenty-four-hour period.

It is felt that, in such cases, the use of a chair or similar apparatus to the one depicted is of considerable value. In the case described, after about three or four days the infant adapted himself to the chair without difficulty and has since remained permanently upright, is contented, and sleeps well.

There does not seen to be any reason for doubt that the ultimate outlook will be similar to that of other cases previously followed—complete recovery from vomiting and even ultimate disappearance of cardio-esophageal reflux radiologically.

SUMMARY

The condition of cardio-chalasia in infancy is discussed, and reference made to literature describing the disease and to the controversial subject of the cardiac sphincter.

It is suggested that this condition may not be as rare as the literature suggests and that the diagnosis might be made more frequently if barium meal x-ray examinations included screening in the Trendelenburg position. In addition, it should probably be segregated from infantile hiatal hernia with esophageal stenosis and the condition of congenital short esophagus. Treatment of cardio-chalasia should be conservative. The use of a chair constructed to maintain an upright posture is demonstrated.

I wish to thank Dr. P. T. Bray for his very valuable advice and help in the management of the case and preparation of this paper; also to the radiologists, Drs. J. H. Stranger and G. Hind, for carrying out the barium meal x-ray examinations.

Acknowledgment is also due to Sister D. N. Roberts for originating the design of the chair, and also to the whole nursing staff of the infants' ward for the excellent care given to the management of the baby.

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ADDENDUM

Since this paper was written, the infant has continued to make satisfactory progress. At one year of age, he weighed 22 pounds. He has been nursed at home normally for the past four months and only vomits small quantities occasionally.

Barium meal and screening was repeated on July 31, 1952. It was not possible to demonstrate any reflux from the stomach into the esophagus even with pressure on the abdomen. No evidence of stenosis, ulceration, or hiatal hernia could be found.

THE SUCCESSFUL TREATMENT OF C. DIPHTHERIAE ACUTE BACTERIAL ENDOCARDITIS WITH CHLORAMPHENICOL, PENICILLIN, AND STREPTOMYCIN

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IN 1949 Almklov and Hansen[1] reviewed seventeen fatal cases of subacute bacterial endocarditis due to *Corynebacterium diphtheriae* and detailed the first successful treatment of a patient with this disease. Their patient, an 8-year-old child, had bacteremia for a virulent strain of *C. diphtheriae* prior to institution of specific therapy. After one month of large doses of penicillin, their patient showed no improvement. When streptomycin was added, there was dramatic improvement.

The following case is presented because of the infrequency and high mortality of acute *C. diphtheriae* bacterial endocarditis.

CASE REPORT

Present Illness.—An 11-year-old white male was admitted to the University Hospital May 13, 1951. The present illness began two days before admission when the patient developed fever, abdominal pain, and vomiting. One day before admission he reported to a physician, complaining of generalized aches, pains, and severe headache. His temperature was 100° F. at that time. He was given penicillin (300,000 units in oil) then and on the day of admission. Temperature elevation as high as 105.8° F. persisted.

Past History.—He received routine immunizations at an early age, including diphtheria toxoid. Growth and development had been normal. Only usual childhood diseases were elicited. There was no historical evidence of heart disease or history of disease compatible with rheumatic fever.

Family History.—The mother and father were both living and well. There were three siblings all of whom were well at the time this patient became ill.

Physical Examination.—He was quiet, well oriented, alert, and cooperative. There were numerous abrasions over the arms and legs. There was no jaundice or cyanosis. The blood pressure in the left arm was 90/65. Respiratory rate was 18. Temperature was 105.2° F. Eyes revealed no petechiae. Funduscopic examination was normal. Ears showed scarred drums which were not inflamed. The neck was supple. There were bilateral, nontender, shotty cervical nodes. The lungs were clear to auscultation and percussion. Examination of the heart revealed normal rate, rhythm, size, and sounds at the time of admission. There were no palpable organs or masses in the abdomen. The extremities were within normal limits. The neurological examination was negative.

Laboratory Examinations.—There were 2,200,100 red blood cells, 16,000 white blood cells, 82 per cent polymorphonuclears; corrected sedimentation rate was 30 mm. in one hour. There was a negative Schick test and negative OT tuberculin test. The serologic test for syphilis was negative. Fasting blood sugar was 88 mg. per cent. Examination of the urine throughout the hospital admission was normal.

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Routine nose and throat and blood cultures were taken on admission and at regular intervals. Nose and throat cultures revealed *Staphylococcus albus*, hemolytic streptococcus, and *Diplococcus pneumoniae*. Blood cultures were subsequently found to be consistently positive for *C. diphtheriae* for the first eight days after admission.

Course in the Hospital.—On the fifth hospital day his temperature was 103° F. He was still complaining of a severe frontal headache. Physical examination was unchanged. The white count at this time was 16,150 with 87 per cent polymorphonuclears. Chest roentgenogram was negative. On the sixth hospital day numerous conjunctival and buccal mucosal petechiae were first noted. Re-examination of the heart at this time revealed a muffled first sound at the mitral area and a high-pitched, apical, systolic murmur. The next day the temperature was still 105° F. A lumbar puncture was done which was negative. Examination of the heart on the eighth hospital day revealed the high-pitched apical murmur still present. During this eight-day period the patient received no antibiotics, and on the eighth day his temperature spiked to 106° F.

The patient was started on aqueous penicillin, 200,000 units, every three hours, intramuscularly. On the ninth hospital day disc type sensitivity studies were done on the organisms and gave the following results:

Streptomycin	Completely resistant.
Penicillin	Moderately sensitive.
Aureomycin, Terramycin, Chloramphenicol	Highly sensitive.

On the tenth day after admission, or two days after beginning penicillin, a marked change in the character of the heart sounds occurred. The muffled first mitral sound was present. A split second sound was present. The mitral murmur was louder, more prolonged, blowing, and of a much lower pitch. On the afternoon of the tenth hospital day the patient suddenly developed pain over the right brachial artery. The entire right arm became cyanotic, and no arterial pulsations were palpable. After five or ten minutes these symptoms improved. On the following day the patient had severe pain in the right inguinal region. The entire leg below the knee became ashen gray, cold, and pulseless. It was evident that emboli had lodged in these regions. The patient was started on Dicumarol therapy. Blood cultures became negative following penicillin therapy, but clinically the patient remained febrile and toxic. Hence chloramphenicol,* 100 mg. per kilogram per day by mouth, was begun on the fifteenth day. Two days following the administration of chloramphenicol a marked clinical improvement was noted. The temperature did not go higher than 101° F. On the seventeenth hospital day he developed a severe pain in his right inguinal region, and it was the impression of the observers that he had developed another embolus in his right inguinal region. Examination at this time revealed that the heart sounds had changed. The systolic murmur was harsher, prolonged, and almost replaced the first mitral sound. Penicillin dosage was decreased to 300,000 units of the repository type every twelve hours. He remained seriously ill. His right thigh was flexed. The tip of the spleen was palpable. Blood pressure was not obtainable in the right arm, but in the left arm it was 96/70. On the eighteenth day the patient had a severe nosebleed. Dicumarol was discontinued, and he was transfused. On the nineteenth hospital day the patient com-

*Chloromycetin was supplied by the Parke, Davis & Company, Detroit.

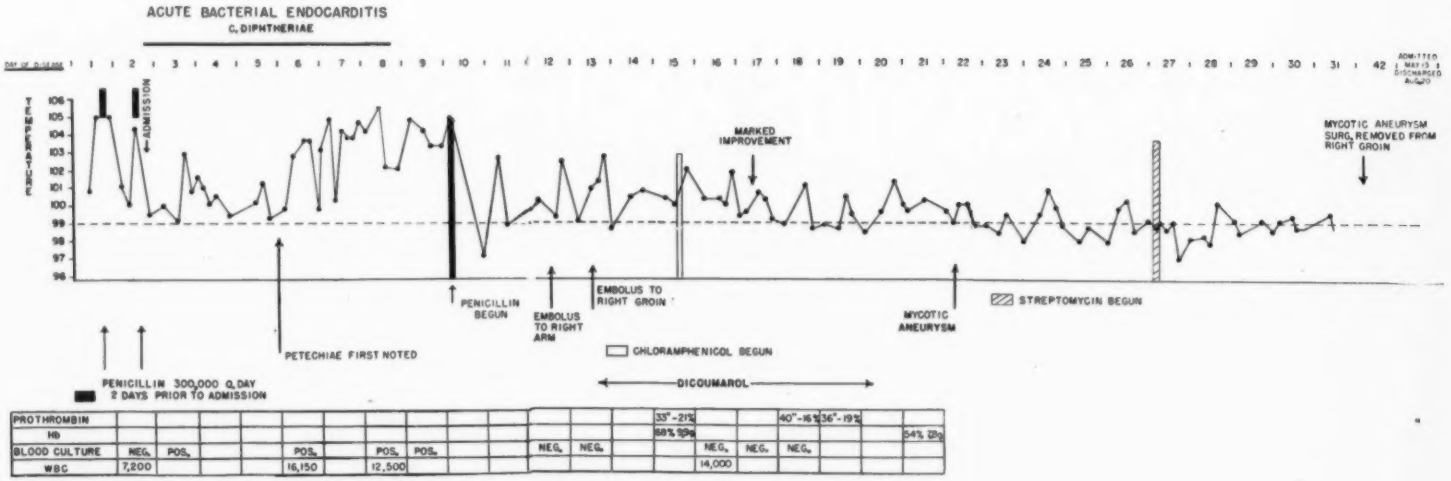
ACUTE BACTERIAL ENDOCARDITIS
C. DIPHTHERIAE
DAY OF DISEASE
ADMITTED MAY 13
DISCHARGED AUG 10
TEMPERATURE
ADMISSION
PENICILLIN 300,000 Q. DAY
2 DAYS PRIOR TO ADMISSION
PETECHIAE FIRST NOTED
PENICILLIN BEGUN
EMBOLUS TO RIGHT ARM
EMBOLUS TO RIGHT GROIN
CHLORAMPHENICOL BEGUN
DICOUMAROL
MARKED IMPROVEMENT
MYCOTIC ANEURYSM
STREPTOMYCIN BEGUN
MYCOTIC ANEURYSM SURG. REMOVED FROM RIGHT GROIN
PROTHROMBIN
Hb
BLOOD CULTURE
WBC
33"-21%
40"-16%
36"-19%
54% 22g
NEG.
POS.
7,200
16,150
12,500
14,000

Fig. 1.

plained of less pain in his right inguinal region, and it was possible to palpate a large pulsating mass which was thought to be a mycotic aneurysm. Electrocardiogram and teleoroentgenogram of the chest were negative. On the twenty-first hospital day the blood pressure in the left arm was 98/60. The heart revealed a grade II systolic mitral murmur. The spleen tip was still palpable. On the twenty-third hospital day numerous petechiae were again noted on the conjunctivae. There was a low-grade fever up to 100.8° F. On the twenty-seventh hospital day 1 Gm. of intramuscular dihydro-streptomycin daily was begun. On the twenty-ninth hospital day moderate clinical improvement was noted. The temperature remained normal from this date.

Examination one month after admission revealed a thrill over the pulmonic area and a systolic mitral murmur. The pulmonic second sound was intensified and split. The aneurysm in his right inguinal region began to enlarge and became soft. Pulsations were not as marked. By the fortieth hospital day the aneurysm was surgically removed. It was small, and surrounded by many lymph nodes and fibrous tissue. Collateral circulation following operation was good. The day following surgery the temperature was 102° F. The forty-second hospital day there was evidence of a thrombophlebitis of the left leg. This subsided spontaneously. On the fiftieth hospital day the patient had been afebrile for one month; penicillin therapy was discontinued. Five days later chloramphenicol was discontinued, and on the sixty-second hospital day streptomycin was discontinued. The patient was allowed up gradually and was discharged from the hospital on the ninety-fifth day in apparently good condition.

Examination at the time of discharge revealed diminished pulsations in the vessels of his leg and in his right arm. Blood pressure could not be obtained in his right arm. The heart examination revealed normal rate, rhythm, and size, but the mitral systolic murmur still persisted. This was very soft and occupied only the middle third of systole. The course of this patient is illustrated in Fig. 1.

Follow-up.—This patient has been seen at three-month intervals for a total of fifteen months. At his last visit interval history revealed that he was leading a normal, active life in school. No subjective numbness, coolness, weakness, or claudication has been elicited in either his right leg or arm. Examination revealed the heart to be normal in size. The rate and rhythm were normal. There was a murmur throughout systole in the mitral area. P_2 was greater than A_2. No diastolic murmur was heard. There were no signs of cardiac decompensation. The right radial artery was not palpable. The dorsalis pedis was bilaterally equal. Collateral circulation to the right arm and leg was good. Nasopharyngeal cultures showed the usual bacterial flora. Electroencephalogram and electrocardiogram were normal. Teleogram of the chest revealed a normal-sized and normal-shaped heart.

DISCUSSION

This case is unusual in that it is the second reported instance of the successful treatment of *C. diphtheriae* endocarditis. There was no history or

evidence that this patient had had a pre-existing cardiac lesion. Damage to the heart caused by the acute infectious process became evident clinically only after repeated examinations. Petechiae and other embolic phenomena were widespread, emboli occurring in the right arm and the right leg. The development of a mycotic aneurysm in the right inguinal region on the eleventh hospital day further complicated his condition. The work of Gunnison,[2] Jawetz,[3] and others which demonstrated the probable synergistic action of penicillin and streptomycin on enterococci prompted us to determine the in vitro sensitivity of the combined drugs against this patient's organisms, *C. diphtheriae*. The organism was grown in broth cultures with varying dilutions of chloramphenicol, streptomycin, and penicillin alone and in combination. A definite synergistic effect was found with combined penicillin and streptomycin. (See Table I.) The sensitivity of the organism to penicillin, chloramphenicol, and streptomycin was within levels usually obtained with dosages outlined for this patient. Clinically, the patient appeared to improve only slightly after the administration of penicillin alone. The blood cultures did, however, become negative. There was notable symptomatic improvement following institution of chloramphenicol, and marked symptomatic improvement with defervescence when streptomycin was combined with penicillin and chloramphenicol. The patient became alert, cooperative, and no further petechiae appeared. In view of the rapid clinical response noted in this patient and in the patient reported by Almklov and Hansen, it appears that the use of a combination of drugs, namely, penicillin, chloramphenicol, and streptomycin, in *C. diphtheriae* endocarditis and septicemia is indicated. Sensitivity tests, using the serial tube dilution method, should be done in each case of endocarditis, no matter what the organism. However, one should never wait for the results of such sensitivities before starting specific treatment. It is interesting that in this patient at no time were any *C. diphtheriae* isolated from the nasopharynx. Penicillin therapy given prior to admission may have resulted in clearing the nasopharynx of this organism.

TABLE I. RESULTS OF IN VITRO SERIAL TUBE DILUTION SENSITIVITY TEST DEMONSTRATING A DEFINITE SYNERGISTIC ACTION OF COMBINED PENICILLIN AND STREPTOMYCIN AGAINST C. DIPHTHERIAE. NO SYNERGISM OCCURRED BETWEEN CHLORAMPHENICOL AND PENICILLIN; HOWEVER, AN ANTAGONISTIC EFFECT WAS NOT NOTED

	C. DIPHTHERIAE	
	GROWTH	COMPLETE INHIBITION
Penicillin (unit/ml.)	0.16	0.625
Chloramphenicol (gamma/ml.)	3.1	6.25
Streptomycin (gamma/ml.)	1,000	None
Combinations Giving Complete Inhibition of Growth		
1.25 units penicillin plus 3.1 gamma chloramphenicol		
0.08 units penicillin plus 50 gamma streptomycin		

SUMMARY

The successful treatment with chloramphenicol, streptomycin and penicillin in a patient with acute *C. diph-*

theriae bacterial endocarditis is reported. In vitro studies on combined drug sensitivities, as well as the clinical response to chloramphenicol, penicillin, and streptomycin in this case, suggest that combined treatment may be beneficial in such cases.

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Medical Progress

HEMOLYTIC ANEMIAS

Mechanisms and Diagnostic Aspects

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NOWHERE in clinical hematology has the influence of basic research made itself felt more strongly in recent years than in the field of hemolytic anemias. New tools which have become available from other disciplines, notably immunology, chemistry, and genetics, have provided improved diagnostic methods and at the same time furthered the understanding of the various hemolytic processes. Even though some fundamental questions remain to be answered, the classification of the hemolytic anemias today rests on a rational basis, and the various disorders can be discussed in terms of physiologic mechanisms.

GENERAL CONSIDERATIONS

The term hemolysis is used in two ways. In the narrower sense it means the actual lysis of erythrocytes by rupture or dissolution of their envelope. In its customary wider sense hemolysis is the term applied to the destruction of red corpuscles in vivo or in vitro regardless of the mechanisms involved. Hemolytic anemias therefore are all those anemias in which the primary event is the exaggerated destruction of blood. Hemoclastic anemia, a term coined by the British school, would be more satisfactory to denote this meaning but will hardly replace the firmly established term, hemolytic anemia.

Hemolysis in its general sense is, of course, a physiologic phenomenon. Red corpuscles do not persist forever but undergo destruction after a period of time which depends on their structure and on their environment. One of the great recent advances in physiology has been the establishment of the life span of the erythrocyte. Under normal conditions the time between the appearance of the red corpuscle in the circulation and its elimination from the blood stream is between 100 and 120 days. Since this figure is one of the fundamental constants in hemolysis it is well to state briefly how it has been established. The most readily available method is the Ashby technique of differential agglutination.[1] Compatible cells which can be identified serologically are transfused into a suitable recipient, for example, group O cells into an individual of group A, or N cells into an M recipient. Subsequently the mixture represented by the recipient's blood is exposed to agglutinating serum, anti-A or anti-M. His own cells will be clumped but the transfused O or N cells will remain unagglutinated and may be counted in the ordinary way.

When serial counts of the transfused cells made in this manner are plotted against time, a linear curve is obtained with the end point at 100 to 120 days.[2] Studies with an entirely independent technique, namely, the tagging of erythrocytes with radioisotopes, N^{15},[3] C^{14},[4] or Fe^{59},[5] which does not involve

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the transfer of cells from one individual to another have given comparable results. The validity of the Ashby method is therefore established beyond reasonable doubt.

The slope of the survival curves indicates a destruction of about 1 per cent of the total red cell mass each day. From this value we can derive the magnitude of the bone marrow performance per day since with the total red cell mass constant production must equal destruction. In terms of hemoglobin produced this means about 7 to 8 grams per day in the adult or the equivalent of 50 c.c. of whole blood.

The straight line survival curve further indicates an orderly, progressive process of red cell destruction from which we may infer that a constant process of ageing is taking place. The nature of this ageing process is not yet clear. The classical theory of Rous[6] postulated that progressive fragmentation occurs as the result of mechanical wear and tear in the circulation. The survival studies indicate, however, that the disappearance of red corpuscles from the circulation is an all-or-none event rather than one of gradual fragmentation. Ponder[7] has suggested that the ageing process corresponds to intrinsic changes within the red cell, a using-up of the enzyme systems and degradation of chemical constituents. In any event Stewart and associates[8] have shown in ingenious experiments involving red cell populations of a single age that after a time the mechanical fragility of erythrocytes increases progressively, and Castle and associates[9] believe that the mechanical trauma causes the disintegration of these susceptible, aged cells. No one knows whether the final event of elimination is lysis, fragmentation, or phagocytosis. Under pathologic conditions all three mechanisms can certainly be utilized.

Physiologic blood destruction, whatever its ultimate mechanisms, is a balanced process in which the loss of old erythrocytes is accompanied by the production of new ones at a constant rate. This equilibrium is reflected in the maintenance of the total red cell count, in the constant proportion of reticulocytes in the total erythrocyte population, and in the fact that the rate of excretion of pigments derived from the breakdown of hemoglobin normally does not exceed certain limits. Exaggerated hemolysis produces characteristic changes in this equilibrium. The expression of this disturbance depends on the rapidity of the hemolytic process and on the functioning of contributory and compensatory mechanisms.

With the increased destruction of erythrocytes the formation of bilirubin from hemoglobin is increased. As long as the rate of bilirubin formation does not exceed the reserve excretory capacity of the liver, the plasma bilirubin level may remain normal or only slightly elevated, and the only evidence of increased breakdown will be an increase in fecal urobilinogen excretion. The measurement of fecal urobilinogen is therefore a valuable indicator of increased hemolysis, especially in the absence of jaundice. We now know, however, that at least 10 to 15 per cent of the pigment excreted in the stools is derived from sources other than the breakdown of hemoglobin. London and co-workers[10] demonstrated the existence of this metabolic by-pass by feeding glycine, a building stone of the porphyrin ring of the heme molecule, which had been

labeled with N^{15}. With this method they showed that a substantial portion of the pigment excreted had never been incorporated in the hemoglobin molecule but had gone through other metabolic pathways. Thus the assumption that urobilinogen excretion furnishes a reliable quantitative measure of hemoglobin breakdown has been disproved. Nevertheless, properly understood in their limitations the urobilinogen measurements are useful. The excretion of normal amounts precludes a major hemolytic process while marked increases usually signify exaggerated blood destruction.

If the breakdown of hemoglobin is rapid or if liver function is impaired as is likely in chronic hemolytic anemias, the excretory capactiy of the liver is exceeded and bilirubin of the so-called indirect variety will accumulate in the plasma, and clinical icterus will appear.

In the presence of sudden intravascular hemolysis there may be no time for the transformation of hemoglobin to bilirubin, and free hemoglobin appears in the plasma. Hemoglobinuria, however, will occur only if the plasma hemoglobin level exceeds the renal threshold of about 150 mg. per cent but, once established, may continue even though the plasma levels have fallen.[11] Hemoglobinemia and hemoglobinuria always point to intravascular hemolysis, a mechanism which at once indicates certain diagnostic possibilities and excludes others. With intravascular hemolysis, degradation of hemoglobin to hematin occurs, and this pigment combines with a plasma fraction to give an abnormal brownish pigment, methemalbumin.[12] The presence of this pigment becomes especially significant when free hemoglobin cannot be demonstrated in the plasma.

Equally as characteristic of hemolysis as the changes in the pigments of plasma and excreta are the changes in the blood and bone marrow. Exaggerated blood destruction is shortly reflected in a fall of the red cell count. The anemia calls forth compensatory hyperactivity of the marrow resulting in erythroid hyperplasia and release of young cells into the blood stream. As long as the hemolytic process is gradual and marrow activity adequate, the anemia may be fully compensated, the total red count will be normal and only the increased proportion of erythroblasts in the marrow and the reticulocytosis of the blood betrays the fact that hemolysis is going on. This is a common situation in mild, compensated asymptomatic congenital hemolytic icterus.

If the process is more severe, not only will anemia be present but the peripheral blood will show more or less striking evidence of rapid regeneration. As young cells with incomplete hemoglobin complement reach the blood stream, polychromasia develops. Since newly formed cells are larger than mature erythrocytes, macrocytosis will occur unless other processes such as sphering counteract this trend. Usually there is some degree of neutrophilic leukocytosis, and the platelets may likewise be increased in number. Nucleated red cells enter the circulating blood, especially when the strain on the marrow organ becomes such that other sites of blood formation are activated. This occurs with special ease in infancy and childhood. Finally, in the congenital anemias, the perpetual demand leads to expansion

of active marrow tissue in the bones with characteristic skeletal changes.

While the so-called regenerative blood picture is typical of hemolytic anemias in general, it has been shown recently that there are important exceptions with which one must be familiar if serious mistakes in diagnosis are to be avoided. Owren[13] has shown that erythropoiesis in the marrow of patients with congenital hemolytic icterus is at times severely depressed or virtually abolished. At such times the peripheral blood picture would also become aplastic rather than regenerative. Only the previous knowledge or subsequent observation can establish the diagnosis of a hemolytic anemia in patients in such an aplastic crisis. The critical fall in red count in such patients results, of course, from a combination of accelerated blood destruction and sudden complete failure of replacement. Owren believes that the so-called hemolytic crisis of congenital hemolytic icterus is in reality an aplastic crisis, or acute erythroblastopenia. Others do not agree but maintain that true hemolytic crises occur apart from aplastic ones.[14] In any event Owren's observations are important, all the more because similar episodes have since been seen in sickle-cell anemia[15] and even in Mediterranean anemia.[16] The mechanism responsible for the sudden but transient cessation of erythropoiesis is still obscure.

In view of such observations it is well to remember that hemolytic anemias represent a dynamic process with changes in equilibrium from time to time. A single "still" picture of blood or bone marrow may fail to illustrate the whole process, and in the study of these conditions repeated observations are often required for an adequate diagnosis. Too often the clinician expects the hematologist to give an opinion based solely on morphologic grounds where in reality a physiologic study is indicated.

The clinical symptoms, like the chemical and hematologic findings, vary with the duration and intensity of the hemolytic process and to some extent with the mechanism. The spleen is enlarged in the great majority of hemolytic anemias because of its predominant role in the hemolytic process itself. There are, however, many hemolytic conditions, not necessarily of minor degree in which splenomegaly is not a feature. This is especially true for sudden intravascular hemolysis as is seen in many acquired toxic anemias due to toxins or poisons. It is well to remember that the acute hemolytic episode itself is likely to produce fever, prostration, vomiting, pain, and leukocytosis. The presence of these symptoms does not prove in itself the presence of infection although this assumption is often made. Such pictures do present considerable difficulties, however, in deciding whether patients with a known hemolytic anemia have a crisis or an acute appendicitis or similar surgical emergencies.

So much for the over-all pattern of hemolytic anemias. Once the fact of accelerated hemolysis has been ascertained, the question of the cause and nature of the process immediately arises. Basically two possibilities can account for accelerated blood destruction. Either the red corpuscles are intrinsically defective and therefore susceptible to destruction even in an essentially normal environment, or extrinsic factors damage previously normal cells and either destroy them di-

rectly or make them susceptible to destruction in the blood stream or in the tissues.

The use of the Ashby technique has greatly clarified this problem and has largely served as the basis for the modern classification of hemolytic anemias into intracorpuscular and extracorpuscular disturbances. Cells which are intrinsically abnormal may have a shortened life span even though their environment is essentially normal. Such cells will therefore be eliminated rapidly, usually in linear fashion when transfused into a normal recipient.[17] Conversely normal erythrocytes transfused into such patients will have normal survival. This pattern is characteristic of the inherited, congenital hemolytic anemias. If, on the other hand, originally normal red corpuscles are destroyed by abnormal lytic mechanisms in blood or tissues, normal cells transfused into the patient will be equally susceptible and their survival, like that of the patient's own cells, is shortened. Such curves are usually curvilinear and indicate that cell destruction is no longer the result of a simple ageing process but is due to an extrinsic event. The patient's own cells, when removed from their pathologic environment and placed in a normal recipient, may survive normally unless they have already been irreversibly damaged. This is the pattern of acquired hemolytic anemias.

INTRACORPUSCULAR DISTURBANCES

The intracorpuscular defects must be related to the physicochemical structure of the red cell. In the three common types of congenital anemia this defect leads to characteristic shape anomalies which facilitate the classification and recognition of these disorders, the congenital spherocyte in congenital hemolytic icterus, the sickle cell in sickle-cell anemia, and the hypochromic microcyte or leptocyte in Mediterranean anemia.

The spherocyte of congenital hemolytic icterus is not a true sphere but an abnormally thick misshapen cell.[18] Because of its deformity it forms rouleaux in the wet drop poorly if at all. In the flat dry smear it appears small, deeply stained, and shows less central pallor than the normal disk-shaped erythrocyte. Its shape prevents the expansion of which the normal cell is capable before rupturing in a hypotonic medium, and its osmotic fragility therefore is increased. This finding is not diagnostic, however, of congenital hemolytic icterus but also occurs when previously normal cells come under the influence of hemolytic agents. Such cells assume a spherical shape before rupturing, the so-called prolytic sphere,[19] and are then unable to tolerate hypotonic environments for the same reason as the congenital spherocyte. Spherocytosis does occur in many acquired hemolytic anemias and is always associated with increased osmotic fragility. It is not specific for congenital hemolytic icterus as was thought at one time.

The well-known test for osmotic fragility of erythrocytes is by no means infallible. There are instances in which the osmotic fragility of individuals known to have congenital hemolytic icterus is normal when the test is performed under standard conditions on freshly drawn blood. Although this fact must be known to every experienced hematologist it has not been sufficiently stressed in the standard texts on the subject and the

student might easily come away with a misleading impression that normal osmotic fragility of erythrocytes rules out the diagnosis of congenital hemolytic icterus. Because so much may depend on the correct evaluation of erythrocyte fragility it is important to realize the technical limitations of the method, especially when performed indifferently in laboratories not especially geared to hematologic problems. Fortunately a valuable addition to the diagnostic techniques has been introduced recently, namely, the study of the osmotic fragility of incubated erythrocytes. The cells to be tested are incubated under sterile conditions for twenty-four hours at 37°. This method is considerably more sensitive than the standard fragility tests and yields positive results where the latter have failed.[20]

The trait for congenital hemolytic anemia appears to be inherited as a single mendelian dominant.[20] Ideally it should always be demonstrable in one of the parents. Family studies are valuable, therefore, in the diagnosis of this as of any hemolytic anemia potentially of congenital type. Sometimes, however, neither parent shows spherocytes or any other abnormality in the blood. In such cases, if impaternity can be excluded, one must fall back on mutation for the explanation of the new trait. The differentiation from an acquired condition may then require elaborate studies including Ashby curves but is usually possible.

The great variability in the clinical picture of congenital hemolytic icterus is well known. In practice only those patients require treatment who have crises or whose anemia interferes with growth or normal activity. Splenectomy is almost 100 per cent successful in this condition. For unknown reasons the spherocytes are trapped selectively in the spleen, not only of the patient, but apparently, after transfusion, in normal individuals.[9] The stasis renders them subject to hypothetical lysins of the local environment. By removing the spleen the trapping mechanism is eliminated, hemolysis is reduced because most of the abnormal cells can now survive for almost the normal life span, and the marrow organ can easily compensate for mild hemolysis. The basic defect remains, however, and the red corpuscles remain misshapen, osmotically fragile, and readily eliminated from the circulation of a normal individual whose spleen is intact.

In sickle-cell anemia the structural defect in the erythrocytes is even more striking. The cells tend to assume a bizarre shape, especially when deprived of oxygen. This phenomenon is usually referred to as sickling but in reality is a more complex and more extreme deformity resulting in long slender filamentous forms. In the unsickled state many cells are target forms. Sickle cells have a decreased osmotic fragility but in a CO_2 atmosphere their mechanical fragility is increased. As might be expected, these abnormal cells have a shortened survival.[21] The exact mode of their destruction in the body is unknown. It may be related to the deformity as such. Sickling undoubtedly occurs in vivo and the sickled erythrocyte may be incapable of passing through capillaries. The resulting stasis not only would enhance sickling by further increasing local anoxia but may well contribute to the development of local lytic mechanisms. Local stasis and

ultimately ensuing thrombosis are also thought to be responsible for the widespread clinical manifestations such as edema and pain in the joints, soft tissues and bone, cerebral episodes, and impairment of circulation elsewhere.[22] The spleen participates in the process but does not play the predominant role it has in congenital hemolytic icterus. Hence splenectomy is usually ineffective although striking amelioration after splenectomy has been noted in a few instances.[23] The patient with sickle-cell anemia eventually splenectomizes himself through repeated episodes of thrombosis and fibrosis.

Sickle-cell anemia must be sharply distinguished from the sickle trait. This distinction has not always been clearly made and at times the impression has been voiced that the trait is a mild form of the disease or may develop into the full-blown anemia. There is now an adequate basis for the statement that the two conditions do not merge but are etiologically, clinically, prognostically separate entities. The trait is clinically asymptomatic. It is not accompanied by anemia or evidence of increased hemolysis. Trait cells sickle less rapidly, less completely, and tend to remain in a true sickle form rather than become filamentous. Trait cells survive normally when transfused into other individuals.

The relationship between the trait and the anemia has been clarified by genetic and chemical studies. Neel[24] has shown that with few exceptions which may have a special explanation, both parents of the patient with sickle-cell anemia sickle, whereas one or both parents of children with the trait show sickling. In other words, the facts indicate that the gene responsible for sickling when present in single dose, combined with a normal gene, produces the trait. In contrast to these asymptomatic heterozygotes, individuals who are homozygous with respect to the sickling gene have sickle-cell anemia.

This concept is in accord with studies by Pauling and associates[25] who showed that sickle hemoglobin migrates with a velocity different from that of normal hemoglobin in the Tiselius apparatus. The structurally abnormal hemoglobin is the predominant component in sickle-cell anemia, and evidently this anomaly is responsible for the sickling phenomenon. In the heterozygous trait, Pauling found two separate components, sickle hemoglobin and normal hemoglobin. These facts correspond to the genetic hypothesis.

In passing, it is of interest to note that sickling cannot usually be demonstrated in the blood of newborn infants,[26] possibly because fetal hemoglobin interferes with the phenomenon. Sickling in infants with sickle-cell anemia may not appear until three or four months after birth. This is also the earliest time for the appearance of symptoms.

In further genetic and clinical studies, patients were found who had a mild hemolytic anemia with sickling, yet who had only one parent with the sickle trait.[27] These individuals did not seem to fit the homozygote-heterozygote theory of Neel and were intermediate, hematologically speaking, between sickle-cell anemia and sickle trait. Electrophoretic analysis showed that in the cells of these patients still another abnormal hemoglobin component was present. This fraction has been tentatively called hemoglobin III.

The trait for hemoglobin III is also genetically determined. In combination with the sickle gene the hemoglobin III trait produces a mild atypical hemolytic anemia. By itself, e.g., in combination with the normal gene, it remains asymptomatic. Such "single heterozygotes" seem to have increased numbers of target cells, however, and, interestingly, their cells are of abnormal hemoglobins and genetic studies become available. Applying the knowledge that fetal hemoglobin is relatively resistant to alkali denaturation, Singer and associates have developed a technique for the demonstration of fetal-like hemoglobin components in a variety of hemolytic states. More recently the same authors used a simple method for demonstrating a

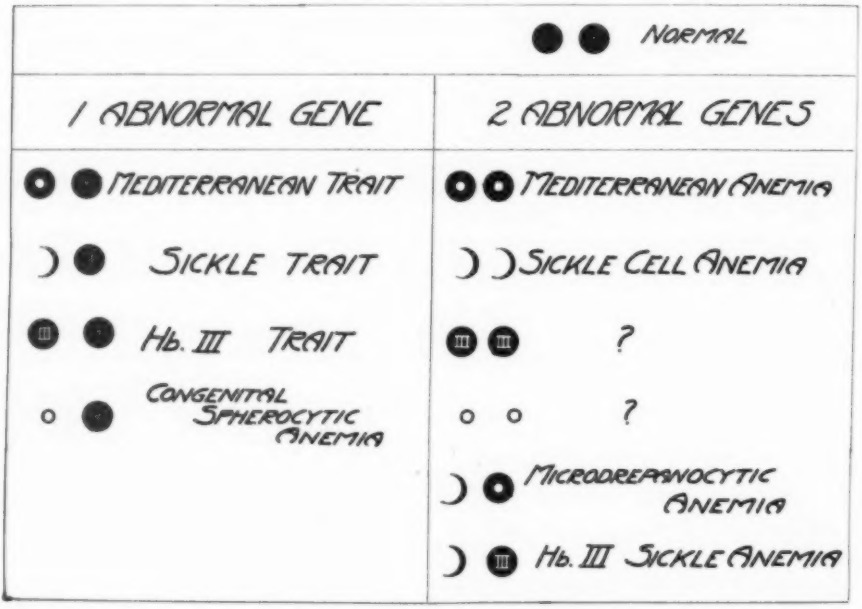

Fig. 1.—A tentative diagrammatic representation of the genetics of inherited intracorpuscular erythrocyte defects.

rapidly eliminated from the circulation of normal subjects. Other combinations of structural defects may produce similar pictures. A combination of sickling and Mediterranean disease trait has already been described.[28] Fig. 1 illustrates the genetics of inherited hemolytic anemias as presently understood.

This whole field is beginning to open up as tools for chemical identification characteristic difference in the solubility of sickle hemoglobin solutions as compared to normal hemoglobin.[29]

Mediterranean anemia represents a genetic situation comparable to sickle-cell anemia. Here, too, the single gene produces an asymptomatic trait, the double gene clinical disease.[30] It seems now generally agreed that the basic abnormality of Mediterranean anemia lies in hemoglobin metabolism

rather than in hemolysis. The red cells do not contain their normal complement of hemoglobin but remain hypochromic and misshapen. Target cells and oval cells are common. The resistance to hypotonic solutions is characteristically increased. Recent studies have shown that there is some shortening of the life span of the abnormal cells in Mediterranean anemia but not in the trait.[31] In the major form there is thus an element of hemolysis.

The trait is widespread in the population of southern Italy and Greece and their descendants in this country. Its most characteristic expression is that of a compensated hemoglobin deficit, e.g., the number of red cells is increased to make up for their relative lack of hemoglobin. This state has been described as hypochromic polycythemia.[32] Sometimes a mild anemia exists which must be differentiated from iron deficiency anemia which it resembles except for a normal or elevated serum iron level.[33] Here again family studies are part of the diagnosis.

In the patient with the major form of the disease, anemia is usually severe and the splenic enlargement, the bone changes, and the blood picture with nucleated red cells reflect the maximum regenerative effort in hemopoiesis. Characteristic is the extreme poikilocytosis, anisocytosis, microcytosis, fragmentation, and hypochromasia. Hemolytic crises do not occur but the prognosis is generally poor and therapeutic success as yet nil. Claims for the beneficial effect of cobalt therapy[34] have not been substantiated thus far.

Apart from these three well-known entities with characteristic shape anomalies there are other genetically determined congential hemolytic anemias which can and must now be differentiated from congenital hemolytic icterus as the new chemical, genetic, and hematologic methods are applied to the study of this whole problem. Already such familial anemias with normal fragility and without shape anomalies have been described.[35, 36] The full delineation of such entities is not as yet possible. Nocturnal paroxysmal hemoglobinuria, a disorder also lacking in characteristic shape changes but characterized by a tendency of red corpuscles to hemolyze when the pH of the blood is lowered, is another inherited anomaly but has never been described in children.

EXTRACORPUSCULAR MECHANISMS

Acquired hemolytic anemias can result from many causes, and a variety of mechanisms may be utilized in their production. The commonest and most readily understood anemia of this type is, of course, malaria in which the parasitic invasion of the red corpuscles is directly responsible for their destruction. Other infectious agents, such as streptococci and *Clostridium welchii*, form products which are hemolytic in vitro and evidently in vivo as well.

The list of chemical poisons capable of producing hemolysis is extensive. Many of these substances are oxidants and produce their lytic effect in vitro or in vivo by either disorganizing the surface structure of the erythrocytes or by disorganizing the internal milieu and metabolism of the cells. Some of these substances are not lytic in vitro. Their effect in vivo then depends on one of two mechanisms. Either a derivative of the original substance with hemolytic action is formed in the in-

ternal metabolism, as, for example, naphthol from ingested naphthalene,[37] or normally sublytic mechanisms in the body are activated by a substance which is not in itself lytic, such as indol.

A practical diagnostic feature of many of the anemias due to exogenous poisons is the development of visible aggregates of denatured substances in the cells, so-called Heinz bodies. These are easily demonstrated in reticulocyte preparations that have not been counterstained. The diagnosis, however, depends chiefly on an accurate history —as was found in studying the anemia due to ingestion of mothballs.[38] Small children are prone to ingest many toxic substances, but the parents may be unaware of the accident or at least of its significance. In naphthalene-induced anemia one finds peculiar segregation of hemoglobin in one part of the cell, a peculiar appearance which is highly suggestive of the diagnosis of hemolysis due to an exogenous chemical poison. The basophilic aggregates and stippling of lead poisoning are well known. Absence of stippling would be strong evidence against a diagnosis of lead intoxication but basophilic stippling is not pathognomonic for this type of anemia. It occurs in many disturbances of erythropoiesis.

Physical injury of red cells, namely, thermal burns, will produce changes in osmotic and mechanical fragility of red cells and leads to more or less massive hemolysis.[39] There is evidence, however, that direct injury of the red cell by heat is not the only mechanism involved in the anemia of burns.[40] Normal erythrocytes transfused into burn patients are also eliminated more rapidly than normal.

The field in which perhaps the greatest advance has been made, both in theory and in practical diagnosis, is that of the hemolytic anemias due to immune body reactions. As early as the turn of the century the French school demonstrated hemolysins in some patients with acquired hemolytic anemia and more recently Dameshek repeated and revived those observations.[41] In the majority of cases, however, hemolysins are not demonstrable. The development of the newer tests for atypical antibodies, arising from the discovery of Rh, is largely responsible for the great strides that have been made.[42] Auto- and isoantibodies are occasionally demonstrable in the serum of patients with immune type hemolytic anemias but the chief tool has been the Coombs test which detects the coating of the patient's cells with antibody globulin.[43]

Three groups of hemolytic conditions due to immune bodies may be distinguished:

(1) Hemolysis of mismatched transfused cells due to natural isoagglutinins. The cause is obvious here but the mechanism is not so clear. Yet this type of hemolysis can serve as a model for perhaps a great many spontaneous hemolytic anemias. The natural anti-A or anti-B agglutinins are not usually hemolytic in themselves. Moreover, hemolysis after a mismatched transfusion is delayed whereas the hemolysins are usually effective immediately.[9] Castle assumes, therefore, that the essential primary mechanism in this type of hemolysis is agglutination with subsequent stasis of red cells in capillaries, especially in those of the spleen. Sequestered in ischemic tissue the cells are subjected to local lytic mechanisms the existence of which has been amply

demonstrated. The mechanical and osmotic fragility of the erythrocytes is measurably increased and they may undergo destruction in situ or at distant places as they are abnormally vulnerable to mechanical injury in the circulation. These considerations have a bearing on the second and third group of immune hemolytic anemias.

(2) In the second group acquired antibodies with specificity against Rh or other erythrocyte antigens are present. The prototype of this group is, of course, erythroblastosis fetalis. In addition to Rh a whole group of new antigens with similar effects have recently been discovered. Anti-A or anti-B erythroblastosis has also been described though the criteria for this condition are as yet unsatisfactory. In an O mother anti-A or anti-B agglutinins will always be present so that recognition of the mechanism of hemolytic disease in the newborn infant due to such antibodies is difficult. The Coombs test, unfortunately, is as a rule negative. Survival studies have shown, however, that in such infants A or B cells are eliminated more rapidly than simultaneously transfused O cells.[44] The practical diagnosis of O-A or O-B erythroblastosis is still largely a matter of exclusion.

In contrast, in typical erythroblastosis the infant's erythrocytes give a positive Coombs test almost by definition, and the diagnosis is rarely a problem. As for mechanisms, hemolysins active in vitro do not occur and here again Castle's theory of agglutination followed by ultimate hemolysis in vivo seems to apply. It is important to realize that the union of antigen and antibody is rather loose and reversible. Cells sensitized artificially with Rh antibody and transfused into a normal Rh-positive individual survive normally,[45] perhaps because the antibody is eluted from the cells in the recipient. The mysterious complication of kernicterus apparently is related to the neonatal state and to the icterus more than to specific antibody effects. At least it has been shown that kernicterus is not specific for erythroblastosis but occurs in a variety of neonatal conditions in which maternal isoimmunization can be excluded.[46]

(3) The third group of immune hemolytic anemias is associated with nonspecific iso- and auto-antibodies, usually demonstrable only with the Coombs test, rarely as agglutinins or hemolysins. This group accounts for many of the so-called acquired hemolytic anemias of the older literature. A special variant of this situation is paroxysmal cold hemoglobinuria in which union of antibody, usually a syphilitic reagin, occurs in the cold and lysis in the presence of complement at body temperature. Here, too, a positive Coombs test has been found. The demonstration of cold hemolysins requires, of course, special procedures, of which the Donath-Landsteiner test is the best known.

The Coombs test is the most valuable tool in determining the presence of an immune type of hemolysis. It would seem that it serves to distinguish clearly immune hemolysis from all other hemolytic anemias. It must be remembered, however, that acquired hemolytic states associated with immune antibodies may become superimposed on other types of anemia, congenital hemolytic or otherwise. Acute episodes of hemoglobinuria have been observed in children with known chronic congenital forms of anemia.[47] In our experience this is comparatively

rare, at least in children. Wright and associates,[48] on the other hand, claim to have found antibodies in a very high proportion of patients with various congenital hemolytic anemias. Pending confirmation or refutation of this recent work, it is our belief that the Coombs test is indeed a crucial test which, properly interpreted, distinguishes acquired hemolytic anemias of immune type from all other anemias. We are only beginning to find out how common these conditions are and what some of the associated diseases may be.

Table I. Schema of Hemolytic Syndromes

INTRACORPUSCULAR DEFECTS HEREDITARY			EXTRACORPUSCULAR DEFECTS NONHEREDITARY		
Patient's cells	Short survival		Short or normal survival		
Normal cells	Normal survival		Short survival		
Coombs	Negative		Positive	Positive or negative	Negative
	TYPICAL MORPHOLOGY	NO TYPICAL MORPHOLOGY	IMMUNE		NONIMMUNE
	Congenital spherocytosis	Paroxysmal noct. Hb.	Rh erythro.	ABO erythro.	Bact. toxins
	Sickel-cell anemia	"Atypical" congenital hemolytic anemias	Parox. cold Hb.	Acquired hemolytic anemia	Metabolic
	Thalassemia major			Transfusion reactions	Chemical poison
	Sickle thalassemia			Favism (?)	Heat
	Sickle Hb. III				Parasites
	Elliptocytosis				

Acquired hemolytic anemia of immune type with nonspecific antibody may be a life-threatening situation. In adults splenectomy is often performed and regarded as a life-saving procedure though the results are somewhat unpredictable. When splenectomy is effective, it is not clear whether it is because a source of antibody has been removed or because a major site of erythrocyte stasis or sequestration has been eliminated. In any event recurrences are common. In children this type of anemia is uncommon. There are reasons to expect that ACTH and cortisone might affect these conditions, and recent reports have indeed shown dramatic improvement after the use of these hormones.[49] Our own experience though limited to a single case has been so favorable that we feel a trial would always be indicated before more drastic measures are resorted to.

With the immune type of anemias we leave the well-characterized hemolytic anemias and enter a field which is still more or less completely obscure. Hemolysis occurs in association with a variety of processes which in some unknown way seem to disturb the balance between the natural plasma or tissue lysins and their inhibitors. Thus anemias which on the surface seem to be accounted for entirely on the basis of deficient red blood cell production have been found to have at least an element of hemolysis. This is true for chronic leukemias in which sometimes striking improvement of the associated anemia is obtained after splenectomy, and in other splenomegalies, in certain tumors, liver disease, and renal insufficiency. To what extent immune mechanisms as yet unrecognized enter

into the production of these anemias, or what other changes take place, we do not as yet know. Recognition of the primary disease is, of course, essential. Only recently Moolten and Clark[50] in a provocative but as yet unsubstantiated report have suggested that certain hemagglutinating viruses can produce hemolytic anemias.

SUMMARY

To sum up, hemolytic anemias are either due to inherited intracorpuscular defects or to extrinsic factors acting on the red corpuscles. Table I gives a graphic summary of the basic features of the main hemolytic syndromes. The common intrinsic defects are characterized by more or less diagnostic shape anomalies. Chemical identification of abnormal hemoglobins or stroma components should soon become a practical diagnostic tool. In doubtful cases erythrocyte survival studies may decide the issue. Among the extracorpuscular hemolytic anemias those due to immune mechanisms can nearly always be separated from all others by the Coombs test. In the majority of the remainder either a direct hemolytic agent, infectious, chemical, or physical, can be elicited, or a primary disease, neoplastic or metabolic, should be looked for. The correct therapy usually flows from the diagnosis.

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Psychologic Aspects of Pediatrics

POSTURAL AND RIGHTING RESPONSES IN CHILDREN

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ALTHOUGH postural and righting reflexes were isolated and described in experimental animals,[1] these responses may be studied clinically in the intact individual. Experimentally, postural reflexes are mainly concerned with changing muscle tone in the maintenance of posture and equilibrium. They are described[2] as (1) those in which the stimulus and the response occur in the same extremity (local static reactions), (2) those in which a stimulus to one extremity affects the extremity of the opposite side (segmental static reactions), and (3) those which arising in one segment affect muscles innervated by other segments (general static reactions). The latter group includes the tonic-neck and tonic labyrinthine reflexes. It is the tonic-neck response which has clinical implication. Experimentally found in oblongata dogs and cats and in midbrain monkeys, the tonic-neck reflex is brought out by rotation of the head. There is, in response, extension of the "jaw" extremity, and flexion of the occipital extremity.

The righting reflexes relate to the orientation of the animal in space and include reflexes in response to stimuli from labyrinths, eyes, neck, and body. The neck righting reflex, clinically important, consists in rotation of the body to follow rotation of the head. For the maintenance of tonic-neck responses, integrity of the medulla is needed, while labyrinthine responses are mediated in the vicinity of the red nucleus.

Clinically, postural and righting responses are not only mediated by medullary and midbrain centers but "there are cerebellar, cortical, and perhaps strio-pallidal influences which change the function of these primary centers."[3] So that in clinical examination we are actually testing the integrated activity of the nervous system, an activity in which psychic factors, too, play a role.

There is, nevertheless, a developmental pattern in postural and righting reflexes. The fetus at twenty weeks is already capable of tonic-neck behavior, and the tonic-neck posture of the infant persisting until about the age of sixteen weeks is well known.[4] Adjustments to maintain the position of the head in the upright position (otolith righting reflex), and adjustments of the head, body, and extremities to linear acceleration (Landau reflex) are normally present by the second month of life. By the end of the first year the child should be able to coordinate the various postural and righting responses to rise from the dorsal recumbent position without assuming the "quadruped position"[5] in which "the head is first rotated, then the shoulders, finally the pelvis

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so as to bring the child almost into the prone position. The body is then erected by use of the arms into the sitting position . . . the legs are extended and the body pushed into the upright position by means of the arms."[6] Retardation in the acquisition of postural adjustment or the retention of fetal patterns is a sensitive index of central nervous system maturation or regression.

Following the work of Hoff and Schilder,[7] postural tests incorporating tonic-neck and neck righting responses have been developed on the Children's Service of Bellevue Psychiatric Hospital. Normal responses in children of varying ages with behavior problems have been sketched by Teicher,[8] and, in addition, the tendency of the child with schizophrenia to whirl on the longitudinal axis has directed our attention particularly to the neck righting response. The method of testing includes:

1. Extension of the arms. When, standing with his eyes closed, the normal adult extends his arms in front of him parallel to each other, the outstretched arms will tend to diverge slightly and symmetrically. Tremor or choreiform movements of the hands are minimal and no postural adjustment of the body is noted. In the normal child, by the age of 5 years, there is usually moderate to marked divergence of the arms, an occasional compensatory lordosis, and moderate choreiform movement to the fingers. One arm is usually held higher than the other. By the age of 8, the posture is more stable and approaches the adult pattern. If, while in the "arms extended" position, the attention of the child is distracted into, for example, counting or reciting the days of the week, abnormalities in postural adjustment escape from volitional control and are more easily observed.

2. Neck righting response. With the patient standing, and with his eyes closed, and the arms extended parallel to each other as in the extension test above, the head is now passively rotated to one side as far as possible without discomfort. Reaction is noted and the head rotated to the other side. In the normal adult, the arms follow the head, with the chin arm extended and slightly elevated and the occipital arm flexed slightly at the elbow and lagging. The body does not rotate with the head. Until the age of 5 to 6 years, however, there is normally a persistence of the neck righting response; there is rotation of the shoulders and hips to follow the movement of the head, and with continuous rotation of the head, the body will rotate on its longitudinal axis. This rotation may, according to Ford,[6] be preceded by an initial counterrotation of the hips. At the age of 5 to 6 years, too, divergence of the outstretched arms is marked with the chin arm distinctly higher. By the age of 8 years rotation of the trunk to follow movement of the head is only infrequently observed, and the position of the arms is similar to that of the adult.

These tests bring out fine abnormalities in postural control and reveal tonic-neck and neck righting responses, which emerge even in the integrated response of the adult. Clinically, the tests as outlined above have maximum value in the child above the age of 5 years.

Abnormal responses commonly seen in extension tests are mainly efforts at

postural control, and consist of: (1) Wide divergence of the outstretched arms or, conversely, convergence of the outstretched arms, (2) marked choreiform movement, (3) efforts at postural control with lordosis, or swaying of the body, (4) synkinesia. Abnormalities of the neck righting response include: (1) Rotation of the body to follow movement of the head. This rotation may be so marked as to constitute an actual whirling about a longitudinal axis. Conversely, there may be extreme rigidity. The patient's head will not rotate even though considerable force may be used. (2) On head rotation, the arms may diverge widely or, conversely, may converge until they overlap. (3) Wide exaggerations of the tonic-neck tendency with extreme flexion of the occipital extremity. (4) Elevation of not the chin extremity but the arm with the dominant muscle tone.

In the study of children with behavior problems observed within the past five years at Bellevue Psychiatric Hospital, these postural tests have been performed routinely and have contributed diagnostic and theoretical insights. In the diagnosis of organic brain disease accompanying behavior disorder, the postural responses are particularly helpful.[9] To a general psychiatric clinic children are brought primarily because of behavior disturbance. The organic factor underlying the behavior disorder is not the obvious or presenting complaint, and indeed in these children neurological signs in terms of tendon reflexes, cranial nerves, motor power, cerebellar signs, and sensory examination of touch, pain, temperature, and pressure are often absent. In these children, classic neurological examination must be supplemented by study of patterned behavior, fluctuations in muscle tone, postural responses and motility. Perceptual and perceptual-motor defects must be investigated, and often projective tests will reveal organic signs. It is in this group of children that postural reflexes may be abnormal in the absence of the more classic neurological signs. Elaine, for example, was 8 years old when her mother brought her to see us with the complaint that "she has so many fears and seems so unhappy." The patient's growth and development were esentially normal except for moderate retardation in motor skills and a general motor awkwardness. On examination, the patient was a chubby, well-developed girl of eight years. She had fears of flushing the toilet, was afraid to go alone from one room to another, and feared the ringing of the doorbell. Neurologically, she was normal except for hyperkinesis and clinging. On postural reflexes, there was wide extension of the outstretched hands with swaying and lordosis. On rotation of the head, there was a wide separation of the outstretched hands with marked flexion of the occipital arm. On psychometric examination, she had an I.Q. of 155 (Stanford-Binet, Form L) with marked variability in performance items, visual-motor difficulty, and manipulation difficulty. The draw-a-man test had organic features. Her electroencephalogram was abnormal with prevalence of slow activity to 2 to 3 cycles per second, occasional paroxysmal fast and hemisphere asymmetry. Hyperventilation response was exaggerated. This case illustrates abnormal postural responses in a child

who is otherwise essentially neurologically intact, but who displays organic signs in perceptual-motor tests and in her psychometric examination.

Descriptively, all varieties of abnormal postural responses may be seen in the "organic" children; marked divergence or convergence of the outstetched arms, synkinesias, almost dystonic efforts at maintaining posture, rotation of the body on its longitudinal axis, and, conversely, extreme rigidity. Differences in postural responses will depend not only upon site, extent, and severity of the organic problem, but also upon the age of the child at its onset and, most important, upon the emotional adjustment the child makes to its disability. There is, in general, no specific postural response to a specific organic condition. Rigid postural responses, however, can be correlated with a suspicious and obsessive compulsive personality.

Stephen, for example, was 9½ years old when he was first brought to see us. He had recurring obsessive thoughts to kill his mother and to kill his father. At the same time he developed a compulsion of having to urinate each time water would touch his hand. His past history revealed that he had been having petit mal episodes since the age of 6 years and sometimes fifty or more such episodes daily. Neurological examination was completely normal but his postural responses displayed extreme rigidity with marked convergence of the outstretched arms and no movement at all in response to rotation of the head. This case illustrates abnormal postural responses in a child with epilepsy and an obsessive-compulsive personality.

We have noted that affect will color the postural response, will change its direction but not its abnormality.

In children with reading disability, studied at the Children's Section of the Mental Hygiene Clinic,[10] it was found that, in general, postural reflexes were immature and less organized than one would expect from the child's age and intelligence level; motility is less static, arm drift is wider, and the body occasionally whirls about the longitudinal axis. Compensatory motor rigidity is occasionally seen. These studies fit in with the concept of reading disability as a maturational lag and significantly relate to the orientation of the body in space. Immature postural responses become part of the syndrome of reading disability which includes faulty right-left orientation, primitive visual-motor Gestalt function, and difficulty in figure background perception.

In schizophrenia, postural responses play an important role not only in diagnosis but also in theoretical formulation. At a descriptive level, the child above the age of 5 to 6 years with schizophrenia will not only have an immaturity in response to the postural reflexes as outlined above, but there is an exaggerated impulse to whirl about the longitudinal axis of the body so that even the slightest passive rotation of the head will set the child into spinning, whirling motion. This motion is fluid and graceful in contrast to the neck righting response of the typical organic child where one has the impression of motor adjustment being made. Below the age of 5 years there are occasional bursts of spontaneous whirling activity, an intense exaggeration of the pleasurable. spontaneous

labyrinthine stimulation of the normal child of 2 to 3 years. When, however, the examiner attempts to rotate the head of the child below the age of 5 years with schizophrenia, extreme resistance may be met. In short, this is just the opposite that one would expect of the normal child of that age.

If, again descriptively, one observes the motility of the child with schizophrenia, there emerges a pattern which has resemblance to old tonic-neck postures. Candid snapshots of these children will catch them in motion and freeze the tonic-neck posture; the head is turned to one side, chin arm is extended, the occipital arm flexed. Serial photographs and movies of children with schizophrenia taken over many years reveal the persistence of this primitive posture and has led Dr. Lauretta Bender[11] to formulate the tonic-neck reflex behavior as a pattern for subsequent motor activity in schizophrenia.

From a theoretical point of view, study of postural and righting response lends support to Lauretta Bender's concept of childhood schizophrenia as an inherent defect in the total biological unit which causes a lag in maturation at the embryological level, with disorder in homeostasis, respiratory patterns, states of consciousness, tissue tonus, and motor activity patterned on primitive tonic-neck reflex behavior. From this fundamental lag in maturation, the secondary problems of identification, body boundaries, and perceptual distortions arise. What the inherent defect is, is unknown.

In relation to postural and righting reflexes in schizophrenia, Schilder[3] said, "It is very difficult to say whether these centers (medullary and midbrain) as such do not function in the right way and whether they are more excitable than they are in the normal person. It may be that these many influences which go to these primitive centers are diminished or increased. I, personally, am inclined to believe that we have to reckon with changes in the primary postural apparatus of the brain as well as the secondary." Psychoanalytic formulations of schizophrenia as a regression to early narcissistic level will include primitive postural reflexes without defining the somatogenic or psychogenic origins of the regression.[12]

SUMMARY

Postural and righting responses may be studied in children by means of an easily performed clinical test. With the patient standing, his eyes closed, the arms are extended parallel to each other. The head is then passively rotated as far as possible without discomfort. Until the age of 5 to 6 years, there may be wide divergence of the outstretched arms, marked choreiform movements, and rotation of the body on its longitudinal axis. Above that age, the posture becomes more static, divergence of the arms minimal, and the body does not rotate with the head.

Abnormal responses above the age of 5 or 6 years consist of exaggerations of the tonic-neck and neck righting responses or, conversely, marked rigidity with convergence of the outstretched arms. Abnormal responses have been found in children with organic brain disturbances, maturational lags, and with schizophrenia.

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Comments on Current Literature

IMMUNITY TO SMALLPOX

RECENT experience indicates that today a significant percentage of the population is not immune to smallpox. In connection with an outbreak of this disease in the city of New York in 1947, mass vaccination was carried out. A survey of the records, made subsequently, led to the general conclusion that only about one-quarter of our population can be expected to have solid immunity. The occurrence of scattered outbreaks of smallpox in various parts of the world, including the United States, would tend to support such a conclusion. A minor epidemic of smallpox which occurred in Brighton, England, during 1950-1951, brought to light the rather surprising fact that, of the entire staff of the isolation hospital, comprising 110 persons, fully one-quarter had never been vaccinated. In this particular outbreak in Brighton, there were twenty-nine confirmed cases; ten of the twenty-nine patients died.

The problem of immunity to smallpox in the present day has been analyzed recently by Benenson, Kempe, and Wheeler[1] in an interesting review entitled, "Problems in Maintaining Immunity to Smallpox." These authors divide the problem into two main categories: first, the problem concerning those individuals who have never been vaccinated, which, while a very important phase of smallpox control, is essentially an administrative responsibility, and second, a category including the relatively larger number —persons who have been vaccinated at some time during their lives, but who have lost to varying degree effective immunity against this serious virus disease.

It has been suggested on several occasions that perhaps new strains of variola virus are being introduced from various parts of the world which are not controlled effectively by inoculation with the strains of vaccinia virus commonly in use for vaccination against smallpox. However, evidence based on experience in the vaccination of military personnel has indicated quite conclusively that such is not the case. Smallpox disappeared completely among the troops after they had been vaccinated with fresh vaccine of proved potency, irrespective of the area in which they were stationed. This observation has been interpreted to mean that Jennerian vaccination is still effective against all strains of variola virus, but that during the course of years, effective immunity wanes, or is lost completely. Careful experimental work with monkeys has substantiated this impression, since potent preparations of standard strains of vaccinia do protect monkeys against different strains of variola.

These authors consider the nature of the vaccinia response an important aspect of vaccination, differentiating carefully the various skin reactions based on sensitivity from those due to actual invasion by the virus. They reemphasize the fact that the procedure of vaccination constitutes a deliberate attempt to bring about infection with a living agent, and point out that the erythematous blush which occurs after the third day following vaccination is an indication of active virus propagation in the local area. This response differs from the redness of skin sensitivity reactions. Where a generalized sensitivity erythema occurs, the reaction is usually evident about the twelfth to fourteenth day following vaccination.

An interesting study is described which was conducted by members of classes at Tufts Medical School. After

careful instruction and "dry-run" practice in multiple-pressure technique, the students were allowed to vaccinate each other. In the first attempt, 22 per cent of the students experienced a "no-take" result. One month later, following further practice, the students repeated the vaccination procedure, and at this time the "no-takes" were observed to be only 9 per cent. Still later by one week, when vaccination procedures were performed by medical staff members only, there was only one "no-take" result among 100 students. Such observations emphasize again the great difficulty experienced in acquiring the proper skill in vaccination technique.

In the review by Benenson, Kempe, and Wheeler attention is drawn also to the fact that vaccine virus deteriorates with time, particularly in warm environments, or on actual exposure to heat, and that vaccine, in order to remain effective, must be kept cold, especially in transit, where exposure to heat is a constant possibility.

In general, these authors conclude that the immune state to vaccinia, and therefore to smallpox, is a relative one, and that, as years intervene following inoculation with active virus, immunity to the disease diminishes. Thus the immune state, once achieved by vaccination, must be maintained by repeated vaccinations. When smallpox was a common disease in the community, this immune state was maintained by repeated contact with variola virus. Since this situation no longer obtains, it is urgent that a sustained effort be made to accomplish revaccination regularly. On the basis of this recent analysis of the problem, it does not appear that vaccinia, as a means of smallpox vaccination, has proved a failure in preventing the disease, but rather that our failure to keep the population at an effectively immune level is responsible for tragic recurrence of smallpox in the highly civilized communities of the world.

Benenson, Kempe, and Wheeler quote from the writings of James Bryce published in 1802. The problem as expressed in these writings seems to apply to our present-day experience, and in this connection it is interesting to read a very timely statement which actually was written four years after Jenner published his original report in 1798.

"Dr. Jenner has thus acted his part; it remains for the other members of society to act theirs; he has shown how important advantages may be obtained; it is theirs to carry this plan into execution by cooperating, both by example and by precept, to render general the practices of inoculation for cowpox: the reward being no less than exterminating one of the most loathsome diseases to which mankind are liable—The smallpox. I must here, however, observe that it is not the prevention of smallpox in a country, for a few years or perhaps a century, that ought to be regarded sufficient. . . . If it should then unfortunately so happen that the advantages resulting from cowpox are forgotten, or undervalued . . . then the smallpox may again be imported from some remote corner where the influence of cowpox was unknown . . . and hold a course among mankind nearly as terrific as that described by authors who relate the ravages of this dreadful disease. . . . Measures might be contrived not only for rendering vaccine inoculation general, but also for continuing it with unremitting diligence throughout future ages."

RUSSELL J. BLATTNER

REFERENCE

1. Benenson, A. S., Kempe, C. H., and Wheeler, R. E.: Problems in Maintaining Immunity to Smallpox, Am. J. Pub. Health 42: 535, 1952.

News and Notes

Dr. Charles F. McKhann has been appointed professor of pediatrics and chairman of the department of pediatrics at the Jefferson Medical School and Hospital.

Dr. A. B. Schwartz has been named acting director of the pediatric department at Marquette University School of Medicine, to succeed the late Dr. Francis Janney.

A **Postgraduate Course** on the **Premature Infant** will be given Nov. 5 through 19, 1952, at the Premature Infant Center of the Charity Hospital in New Orleans. The faculty will consist of members of the Tulane and Louisiana State Medical Schools and the Louisiana State Department of Health. Limited to 10. No tuition fee. Further information may be obtained from Dr. Elaine Allen, Director of the Premature Center at Charity Hospital.

Book Reviews

Allergic Pruritus, Its Dermatologic Management. Stephan Epstein, M.D., St. Paul, Minn., Bruce Publishing Co., 76 pages. Price $2.50.

This small volume, edited by Dr. S. Epstein, is a collection of nine papers presented in 1950 at a panel discussion on "Itching Dermatoses." Individual contributions have been brought up to date, including an added discussion on the current uses of steroid therapy in dermatologic disorders. The volume contains practical therapeutic information for all physicians confronted by dermatologic disorders characterized by pruritus. Effective symptomatic and specific treatment suggestions are based on firm physiologic principles and contraindications to certain forms of therapy are reviewed. The editor has rightfully included a helpful section on the emotional aspects of pruritic disorders.

FRED M. TAYLOR.

Congenital Dysplasia of the Hip Joint and Sequelae. Vernon L. Hart, M.D., Springfield, Ill., Charles C Thomas, 136 pages.

This monograph will give a tremendous stimulus to the early recognition of the congenital hip. The subject is presented with unusual clarity. Diagnostic signs are presented with simplicity. Diagrams and roentgen rays are exceptionally well demonstrated and easily interpreted. To one of the most difficult problems in orthopedic surgery, it gives an air of optimism.

B. F. BOYLSTON.

Advances in Pediatrics. Edited by S. Z. Levine, M.D., vol. 5, Chicago, 1952, Year Book Publishers, Inc., 273 pages. Price $7.00.

After a lapse of two years, *Advances in Pediatrics* reappears under the aegis of a new publisher. The present volume contains six monographs, three from the United States and three from the Scandinavian countries. The first monograph by Dr. Hattie E. Alexander is a discussion of the current methods of therapy for bacterial meningitis which has been undergoing many changes in recent years with the introduction of new antibiotics. It is perhaps the most valuable of the monographs for the practitioner. Dr. Henry Barnett and his associates contribute an excellent discussion of "The Nephritic Syndrome in Children." They discuss the various concepts as to the classification and etiology of the syndrome, and the recent advances in treatment and the place of ACTH. The remaining monographs are of less general interest. Dr. Dam and his associates at Copenhagen discuss vitamin K deficiency and its relation to hemorrhagic disease of the newborn; Dr. Lind of Stockholm, the technique and value of angiocardiographic studies; Dr. Carl H. Smith and associates of New York, iron metabolism in children; and Dr. Arvid Wallgren, BCG vaccination. All of the authors are recognized as authorities in their particular field due to their personal studies and investigations. It is an excellent volume.

Editor's Column

LOBAR EMPHYSEMA IN INFANCY

THREE reports within the last year of cases of lobar emphysema in young infants raise some interesting questions, and dramatically depict the tremendous progress made in thoracic surgery and in pediatric anesthesiology in recent years. In this issue Fischer reports five cases and cites a sixth from the Cook County Hospital in Chicago. Within the year Robertson and James have reported three cases collected from pediatric and thoracic surgery services in Seattle, Portland, and Vancouver, and Shaw of Dallas has added another case in an infant. Thus ten cases in young infants have been reported in which the diagnosis was made from the physical findings and roentgenologic examination. All made a brilliant and rapid recovery following such a major surgical operation as lobectomy.

Seemingly the causative factor of the ball valve obstruction which produces the emphysema—similar to that seen with foreign body obstruction to a bronchus—is some congenital anomaly. Thus soft or weakened bronchial rings, obstructing folds of bronchial mucous membrane, and obstruction by a fibrosed aberrant ductus arteriosus were described in the reported cases as probable causes of the emphysema.

From the pathologic findings it is difficult to argue that for some reason or other the condition has suddenly become prevalent. Nor does it seem likely that it is a condition which if left alone automatically corrects itself as the infant grows older. The more reasonable explanation is rather that we have been missing the diagnosis of a condition which is amenable to the brilliant advances of thoracic surgery.

REFERENCES

Fischer: J. PEDIAT. **41**: 403, 1952.
Lewis and Potts: J. Thoracic Surg. **21**: 438, 1951.
Robertson and James: Pediatrics **8**: 795, 1951.
Shaw: Pediatrics **9**: 220, 1952.

WHAT HAPPENS TO THE ASTHMATIC CHILD?

WILL he outgrow the asthma? Will he have it all his life? These, or questions of a similar intent, are always in the minds of the parents of a child with asthma. A series of 449 patients who developed asthma and were treated by Rackemann* in childhood forms the basis of an interesting follow-up study after twenty years which should be of help in answering some of the questions of worried parents.

In the series, boys outnumbered girls by a ratio of 2 to 1, but there was no sex difference in the outcome. One

*Rackemann, F. M., and Edwards, M. C.: New England J. Med. **246**: 815, 858, 1952.

hundred thirty-eight (30.7 per cent) were found entirely relieved of symptoms and hence appear as "cured," and eighty-seven (19.3 per cent) were relieved of active symptoms but were still "sensitive." Another group of ninety-six (21.4 per cent) were found free of the asthma but had developed other allergies, chiefly hay fever. Thus nearly three-fourths of the children had become free of the asthma in their teens. In Rackemann's opinion it is not a matter of "outgrowing" the asthma, but rather "The age of 'cure' depends on the promptness with which the specific allergenic substances can be found and removed." Death from asthma had occurred in only four of the 449 patients. In Rackemann's report the cases and their outcome are tabulated according to the cause of the asthma.

CAUSES	NO.	(%)	"CURED"	RELIEVED STILL SENSITIVE	OTHER ALLERGIES
Animal	114	(25.8)	19	55	17
Food	36	(8.1)	16	10	6
Pollens	21	(4.7)	4	0	0
Mixed and unidentified	199	(43.3)	50	22	60
Negative tests: "bacterial"	79	(17.9)	49	0	13
	449		138	87	96
			30.7%	19.3%	21.4%

It will be noted that a higher percentage of "cures" was found in the "negative test" and food groups than in those where the asthma was due to animal, pollens, or to "mixed and unidentified causes." However, if the number in the "relieved: still sensitive" group, and those free from asthma but with new allergies are added to the "cures" in each group, there is little difference except in the group due to pollens. Asthma in a child due to a pollen seemingly has the poorest prognosis so far as relief of the asthma is concerned.

Some of the sixteen "cured" patients whose asthma was due to animal contact were given active treatment, while in others the cure was apparently brought about by simply disposing of the offending animal. A much larger group, fifty-five, whose asthma was due to animal contact, are still sensitive, but remain clinically free because they avoid contact. In only thirty-six children, 8 per cent of the total, were foods as eggs and fish responsible. The least frequent cause was pollens, despite the fact that hay fever due to pollens is common in childhood.

To the largest group in the series (199, or 43.3 per cent) Rackemann applies the title of "mixed and unidentified" to the cause of the asthma. Various positive reactions occurred in this group to animal dander, foods, and pollens, but it was not possible to relate these accurately with the development of asthmatic symptoms. The percentage of asthma "cures" in this group was high, but many were found to still be sensitive, or to have developed other manifestations of allergy as hay fever.

In these four groups there were 370 of the 449 children who gave positive skin tests of one kind or another in childhood. A fifth group of seventy-

nine asthmatic children showed no reaction to any of the common foods or dust. In twenty-five of these the dominant clinical features were head colds and bronchitis. Rackemann considers that in this group the asthma was perhaps "bacterial" in origin. Removal of tonsils in seventeen was of no benefit. Some were given vaccines, but a "cure" in these patients took place several years later and the "cure" cannot be ascribed to any specific factor. A number of the children in this group improved with environmental change, which Rackemann considers as indicating a basic allergy.

Considering the series as a whole, about a third of the children became free of their asthma at the average age of 15, and the initial cause of the symptoms, as dust, foods, etc., ceased to be harmful. In addition, 20 per cent are quite well when they reach their late twenties, but must avoid the special factor which brought about the asthma. Another 20 per cent no longer have asthma, but have developed some other manifestation of allergy as hay fever.

These are the general facts that can be told to the parents of an asthmatic child as to the prognosis of the asthma. It does not, however, enable the physician to prognosticate about the specific child, which is the important question to the child's parents. It will, however, help them a great deal to know that so many asthmatic children are free of the symptoms twenty years later.